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Second variation of the energy functional for adhering vesicles in two space dimensions

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Abstract

Computing the second variation of the energy functional of a lipid vesicle is an issue that precedes any local stability analysis. This issue becomes technically more delicate when the equilibrium configurations to be perturbed are partially adhered to a fixed substrate. Within a two-dimensional model, we introduce here a method that delivers the second variation of the energy functional for vesicles subject to adhesion. The formula thus obtained is then applied to estimate the maximum susceptibility to detachment of tubules, hollow vesicles that do not enclose a prescribed volume. In particular, we illuminate by example the role of the substrate curvature in enhancing or depressing the susceptibility of adhered tubules to a special class of detaching fluctuations.

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1. Introduction

Lipid membranes consist of *amphiphilic* molecules organized in bilayers. In particular, the *vesicles* are lipid membranes that can be represented as closed surfaces in the ordinary Euclidean space: among them, *tubules* denote hollow cylinders. The equilibrium of vesicles in general has extensively been explored in the last two decades; its study has revealed a wealth of equilibrium shapes within different models for the membrane elasticity: the interested reader is referred to [1] for a review of these models. In fact, vesicles undergo amazing shape transitions depending on parameters such as the ratio between the area of the vesicle and the enclosed volume, the spontaneous curvature of the membrane, which is a bias for its bending, and the pressure difference between the outer and the inner liquids. Since the equilibrium of vesicles depends on several such control parameters, it is natural to study the stability of the vesicle shapes against changes in these parameters. Thus, both Peterson [2, 3] and Ou-Yang and Helfrich [4, 5] computed independently the second variation of the elastic energy of a *free* vesicle. Later on, Bukman *et al* [6] employed the same format as Ou-Yang and Helfrich's to study the stability of tethered vesicles, applying the area-difference elasticity model (see, e.g. p 34 of [1]) to describe the elasticity of the vesicle.

In general, vesicles are *constrained* systems, as they obey requirements dictated by their physical properties. First, the area of the bounding membrane cannot vary because the membrane is *inextensible* to a good approximation. A further, but less restrictive constraint concerns the volume enclosed by the membrane, which mirrors the membrane impermeability. Assessing the stability of a constrained system involves some mathematical subtleties since the admissible variations must obey all constraints up to *second order*, and this cannot be ensured by the usual technique of Lagrange multipliers, as was apparently first remarked by Lündstrom (see section 41 of Bolza's book [7]). An instructive example of the erroneous application of Lagrange multipliers in computing the second variation of a constrained functional was pointed out by Barbosa and do Carmo [8] in their study of the stability of (hyper)surfaces with constant mean curvature and prescribed enclosed volume: 'if the perturbations were not properly selected, spheres would not be stable'.

Likewise, the constraints to which free vesicles are subject in space make the second variation of the elastic energy functional delicate to compute. Ou-Yang and Helfrich in [5] enforced the relevant constraints up to second order by expanding the shape perturbations on a suitable basis of functions and by expressing the relevant coefficients in the expansion as functions of the remaining ones, thus indeed restricting the class of admissible perturbations. However, since such an expansion resorts to a specific class of functions, one wonders whether the resulting class of admissible perturbations is indeed the most general one can envisage.

A similar criticism can be applied to Peterson's work on the stability of red blood cells [2, 3], though he employs yet another method to handle the constraints. Let n be the normal displacement of a red blood cell membrane. The second variation of the elastic energy is a quadratic form of n, restrained by both the area and volume constraints. Borrowing the language of perturbation theory, n can be split as

$$n = n_1 + n_2$$

where n_1 is a *first-order* perturbation, and $n_2 = O\left(n_1^2\right)$ is an additional perturbation chosen to enforce the constraints up to *second order*. Thus the membrane deformation at the lowest order is parametrized by n_1, but the expansion of the elastic energy contains quadratic contributions from both second-order terms in n_1 and first-order terms in n_2 (cf [3]).

To our knowledge, the available studies on the stability of lipid membranes concern membranes *free* to fluctuate in space, subject only to the constraints on the area and the enclosed volume. Here, we treat lipid membranes that partially *adhere* to a fixed substrate and our approach to the stability of vesicles is different. Pursuing the line of thoughts already traced in [9], we endeavour to study the effect of the adhesion to a rigid substrate on the stability of vesicles in two space dimensions: we pay a price to simplicity in describing the vesicle as a planar, closed curve—for instance, in two space dimensions the energy associated with the spontaneous curvature does not depend on the shape of the vesicle, which thus hides a basic feature of the bilayer lipid architecture. In any event, our model would be more realistic for straight tubules, which in most applications can accurately be described by their cross-section, indeed a curve in two space dimensions. Here, for simplicity, we extend this model to all vesicles: in this we are not unprecedented as a similar model was employed in [10], though a general stability analysis was missing there. We think that the outcomes of our study could also shed light on the stability of adhering vesicles in the three-dimensional space, which is still an unresolved question. A similar motivation is behind the study of the equilibrium configurations of the *elastica hypoarealis* in [11].

The presence of an adhesive wall places a kinematic constraint on the admissible equilibrium configurations of a vesicle, especially when the wall is curved (see, for example [12, 13]). Under this further constraint, we compute the second variation of the elastic energy functional for vesicles adhering on an arbitrarily curved wall, which is accordingly described as a planar contour, whose varying curvature may influence the total adhesive effect on the vesicle.

The admissible perturbations of the closed contour representing an adhering vesicle in two space dimensions must make it *glide* up to *second order* along the substrate to which it adheres. In general, this requires perturbations to be split into first- and second-order components, in the spirit of Peterson's approach. At variance with this, however, the contour displacement cannot be normal along the substrate. As also noted in [15], tangential displacements do yield contributions to the second variation of the energy whenever the vesicle possesses non-trivial borders.

The *detachment points* of the vesicles, that is, the points where the vesicle loses contact with the substrate, are the very protagonists of our stability analysis. The second variation of the energy functional contains two antagonistic contributions: one is integrated along the free part of the vesicle, and the other is concentrated on its detachment points. The balance between these terms determines whether an equilibrium configuration is actually stable or not.

This paper is organized as follows. Section 2 contains a detailed derivation of the second variation of the energy functional, where the role of adhesion is especially illuminated. In particular, the condition that must be imposed to preserve contact between vesicle and substrate up to second order is discussed in detail. In section 3, we derive from the second variation of the elastic-energy functional an integral identity valid for all equilibrium shapes of a free vesicle in two space dimensions. In section 4, we consider an adhering tubule, for which the area enclosed by the planar cross-section is not constrained. We profit here from the knowledge of the exact equilibrium solution to compute explicitly the second variation. For the cases we examine, it is already known that there is a unique equilibrium solution, and so it is little surprise that this solution is stable. However, our study explores the role of the substrate geometry in the vesicle susceptibility to fluctuations: it suggests that the most efficient way to destabilize an adhering tubule is through fluctuations with the largest possible wavelength. On the other hand, the shape susceptibility tends to vanish for fluctuations concentrated at the detachment points. Finally, section 5 summarizes the outcomes of our work. Two appendices with some technical results then close the paper.

2. Second variation of the energy functional

A vesicle in two space dimensions is represented by a planar curve c that possesses a fixed length L and encloses a fixed area A. Accordingly, a rigid adhering substrate is represented by another planar curve. When the vesicle adheres partially to the substrate, the curve c can be regarded as the union of two curves, the *adhering* curve c_*, where c is in contact with the substrate, and the *free* curve c^*, where c is not in contact with the substrate. We call $\mathcal{D}$ the set of all detachment points, that is, the points of the substrate where the possibly disjoint arcs of c_* and c^* meet. We assume that the number of points in $\mathcal{D}$ is finite in all admissible configurations of c and that no arc of c_* is degenerate to a single point. Below, for simplicity, we take $\mathcal{D} = \{p_1, p_2\}$. At the end of the section, we shall easily extend our main result to a general set $\mathcal{D}$ by introducing an appropriate convention on the local orientation of c at its detachment points.

We define the *intrinsic frame* $\{\boldsymbol{t}, \boldsymbol{\nu}\}$ along c by supplementing the unit tangent vector $\boldsymbol{t}$ to c with the inward unit normal vector $\boldsymbol{\nu}$ (see figure 1). Hereafter, s denotes the arc-length along

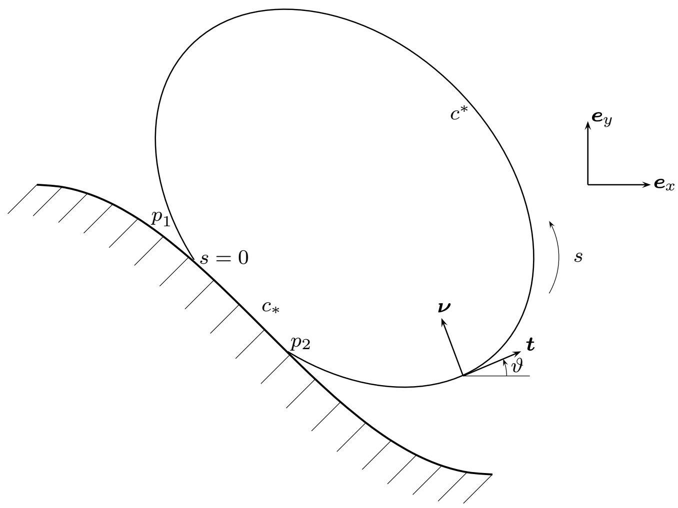

Figure 1. Sketch of a vesicle in two space dimensions adhering to a fixed substrate: c^* is the free curve and c_* is the adhering curve. The set $\mathcal{D}$ of the detachment points consists of $\{p_1, p_2\}$.

c with origin, say, in p_1 and orientation from p_1 to p_2. Relative to the fixed frame $\{\boldsymbol{e}_x, \boldsymbol{e}_y\}$, we can write

$$\boldsymbol{t} = \cos\vartheta\, \boldsymbol{e}_x + \sin\vartheta\, \boldsymbol{e}_y \tag{2.1}$$

and

$$\boldsymbol{\nu} = -\sin\vartheta\, \boldsymbol{e}_x + \cos\vartheta\, \boldsymbol{e}_y \tag{2.2}$$

where $\vartheta(s)$ is the angle between $\boldsymbol{e}_x$ and $\boldsymbol{t}(s)$. For future use, we recall the Frénet–Serret formulae that express the rate of variation of the intrinsic frame along c:

$$\boldsymbol{t}' = \sigma\boldsymbol{\nu} \qquad \text{and} \qquad \boldsymbol{\nu}' = -\sigma\boldsymbol{t} \tag{2.3}$$

where

$$\sigma := \vartheta' \tag{2.4}$$

is the *curvature* of c, and a prime denotes differentiation with respect to s.

The elastic energy $\mathcal{F}_e[c]$ of a vesicle can be expressed in this two-dimensional model by the functional

$$\mathcal{F}_e[c] := \int_c \psi(\sigma)\,\mathrm{d}s \tag{2.5}$$

where the energy density ψ is a smooth function of the curvature σ of c. Whenever the vesicle is in contact with a substrate, an extra adhesion energy $\mathcal{F}_a$ must be added to $\mathcal{F}_e$. We consider the simplest model for adhesion, within which $\mathcal{F}_a$ is taken to be proportional to the length of the adhering curve c_* (see [10, 14]):

$$\mathcal{F}_a[c] := -w\ \text{length}\ (c_*) \tag{2.6}$$

where the positive constant w is a constitutive parameter called the *adhesion potential*. Hence, the total energy functional is expressed as

$$\mathcal{F}[c] := \mathcal{F}_e[c] + \mathcal{F}_a[c] = \int_{c^*} \psi(\sigma)\,\mathrm{d}s + \int_{c_*} (\psi(\sigma) - w)\,\mathrm{d}s. \tag{2.7}$$

The area enclosed by c, which is soon to be prescribed as a constraint, is given by the functional

$$\mathcal{A}[c] := \frac{1}{2}\int_c (p-o)\cdot\boldsymbol{\nu}\,\mathrm{d}s \tag{2.8}$$

where p is the current point on the curve c and o is any point in the plane of c.

Here, we are concerned with the local stability of the equilibrium configurations for $\mathcal{F}$ subject to the constraints on the total length and the enclosed area. We thus compute the second variation of $\mathcal{F}$, ensuring that both relevant constraints are satisfied up to second order. To this aim, we perturb an admissible curve c by deforming it into the curve c_ε according to the mapping

$$p \mapsto p_\varepsilon := p + \varepsilon\boldsymbol{u} + \varepsilon^2\boldsymbol{v} \tag{2.9}$$

where $\boldsymbol{u}$ and $\boldsymbol{v}$ are vector fields of class C^1 along the whole c that represent the first- and second-order variations of c, respectively. They are also supposed to be of class C^2 on c_* and c^*, separately. A similar perturbation was also employed by Peterson in [3] to study the stability of red blood cells, though no adhesion was ever considered in his approach. By repeating almost *verbatim* the analysis explained in [17], and also exploited in [9], it is possible to show that the unit tangent and the normal vectors $\boldsymbol{t}_\varepsilon$ and $\boldsymbol{\nu}_\varepsilon$ to c_ε are given by

$$\boldsymbol{t}_\varepsilon = \boldsymbol{t} + \varepsilon(\boldsymbol{u}'\cdot\boldsymbol{\nu})\boldsymbol{\nu} + \varepsilon^2\big[(\boldsymbol{v}'\cdot\boldsymbol{\nu})\boldsymbol{\nu} - (\boldsymbol{u}'\cdot\boldsymbol{t})(\boldsymbol{u}'\cdot\boldsymbol{\nu})\boldsymbol{\nu} - \tfrac{1}{2}(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2\boldsymbol{t}\big] + O(\varepsilon^3) \tag{2.10}$$

$$\boldsymbol{\nu}_\varepsilon = \boldsymbol{\nu} - \varepsilon(\boldsymbol{u}'\cdot\boldsymbol{\nu})\boldsymbol{t} + \varepsilon^2\big[-(\boldsymbol{v}'\cdot\boldsymbol{\nu})\boldsymbol{t} + (\boldsymbol{u}'\cdot\boldsymbol{t})(\boldsymbol{u}'\cdot\boldsymbol{\nu})\boldsymbol{t} - \tfrac{1}{2}(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2\boldsymbol{\nu}\big] + O(\varepsilon^3) \tag{2.11}$$

accordingly the curvature σ_ε of c_ε is

$$\begin{aligned}\sigma_\varepsilon = \sigma &+ \varepsilon[(\boldsymbol{u}'\cdot\boldsymbol{\nu})' - \sigma(\boldsymbol{u}'\cdot\boldsymbol{t})] + \varepsilon^2\{(\boldsymbol{v}'\cdot\boldsymbol{\nu})' - \sigma(\boldsymbol{v}'\cdot\boldsymbol{t})\} + \sigma(\boldsymbol{u}'\cdot\boldsymbol{t})^2 \\ &- \tfrac{1}{2}\sigma(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2 - (\boldsymbol{u}'\cdot\boldsymbol{t})(\boldsymbol{u}'\cdot\boldsymbol{\nu})' - [(\boldsymbol{u}'\cdot\boldsymbol{t})(\boldsymbol{u}'\cdot\boldsymbol{\nu})]'\} + O(\varepsilon^3)\end{aligned} \tag{2.12}$$

and, finally, the arc-length s_ε along c_ε satisfies the equation

$$\frac{\mathrm{d}s_\varepsilon}{\mathrm{d}s} = 1 + \varepsilon\boldsymbol{u}'\cdot\boldsymbol{t} + \varepsilon^2\left[\boldsymbol{v}'\cdot\boldsymbol{t} + \frac{1}{2}(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2\right] + O(\varepsilon^3). \tag{2.13}$$

To enforce the inextensibility of c, we require that the length of c remains constant up to second order in ε. By (2.13), this amounts to imposing the following integral constraints on the fields $\boldsymbol{u}$ and $\boldsymbol{v}$:

$$\int_c \boldsymbol{u}'\cdot\boldsymbol{t}\,\mathrm{d}s = 0 \qquad \int_c\left\{\boldsymbol{v}'\cdot\boldsymbol{t} + \frac{1}{2}(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2\right\}\mathrm{d}s = 0. \tag{2.14}$$

Moreover, it follows from (2.9) and (2.11) that

$$\mathcal{A}[c_\varepsilon] = \mathcal{A}[c] + \varepsilon\int_c \boldsymbol{u}\cdot\boldsymbol{\nu}\,\mathrm{d}s + \varepsilon^2\int_c\left\{\boldsymbol{v}\cdot\boldsymbol{\nu} + \frac{1}{2}[(\boldsymbol{u}\cdot\boldsymbol{\nu})(\boldsymbol{u}'\cdot\boldsymbol{t}) - (\boldsymbol{u}'\cdot\boldsymbol{\nu})(\boldsymbol{u}\cdot\boldsymbol{t})]\right\}\mathrm{d}s \tag{2.15}$$

and so requiring that the area enclosed by c remains unperturbed up to second order in ε amounts to requiring that

$$\int_c \boldsymbol{u}\cdot\boldsymbol{\nu}\,\mathrm{d}s = 0 \qquad\text{and}\qquad \int_c\left\{\boldsymbol{v}\cdot\boldsymbol{\nu} + \frac{1}{2}[(\boldsymbol{u}\cdot\boldsymbol{\nu})(\boldsymbol{u}'\cdot\boldsymbol{t}) - (\boldsymbol{u}'\cdot\boldsymbol{\nu})(\boldsymbol{u}\cdot\boldsymbol{t})]\right\}\mathrm{d}s = 0. \tag{2.16}$$

A further constraint for c arises from requiring that c_* stays in contact with the substrate under the deformation (2.9): we imagine that c_* can only glide on the substrate and it cannot be torn up. It is shown in appendix A that this condition for c_* is satisfied, provided that

$$\boldsymbol{\nu}\cdot\boldsymbol{u} = 0 \qquad\text{and}\qquad \boldsymbol{v}\cdot\boldsymbol{\nu} + \tfrac{1}{2}\sigma(\boldsymbol{u}\cdot\boldsymbol{t})^2 = 0 \quad\text{along } c_*. \tag{2.17}$$

Thus, while the tangential components of $\boldsymbol{u}$ and $\boldsymbol{v}$ are arbitrary on c_*, their normal components are constrained. As proved in [17], at equilibrium the curvature σ of c suffers a jump at each detachment point, whereas the intrinsic frame of c is continuous there. In view of (2.13), our assumption on the continuity of both $\boldsymbol{u}'$ and $\boldsymbol{v}'$ at all points of $\mathcal{D}$ entails the continuity of the dilation factor $\frac{\mathrm{d}s_\varepsilon}{\mathrm{d}s}$, which is a measure of strain.

For future use, it is expedient to decompose the fields $\boldsymbol{u}$ and $\boldsymbol{v}$ along the intrinsic frame, so that

$$\boldsymbol{u} = u_t\boldsymbol{t} + u_\nu\boldsymbol{\nu} \qquad \boldsymbol{v} = v_t\boldsymbol{t} + v_\nu\boldsymbol{\nu}. \tag{2.18}$$

Accordingly

$$\boldsymbol{u}' = (u_t' - \sigma u_\nu)\boldsymbol{t} + (u_\nu' + \sigma u_t)\boldsymbol{\nu} \qquad \boldsymbol{v}' = (v_t' - \sigma v_\nu)\boldsymbol{t} + (v_\nu' + \sigma v_t)\boldsymbol{\nu} \tag{2.19}$$

where use has also been made of (2.3). An integration by parts and use of (2.19) in both integrals in (2.14) reduce them to

$$\int_{c^*} \sigma u_\nu \,\mathrm{d}s = 0 \qquad \int_{c^*} \left\{\frac{1}{2}(\sigma u_t + u_\nu')^2 - \sigma v_\nu\right\} \mathrm{d}s = 0 \tag{2.20}$$

which are now extended to c^* only. Likewise, the integrals in (2.16) become, respectively,

$$\int_{c^*} u_\nu \,\mathrm{d}s = 0 \qquad \text{and} \qquad \int_{c^*} \left\{v_\nu - \frac{1}{2}\left[\sigma\left(u_t^2 + u_\nu^2\right) + u_t u_\nu' - u_\nu u_t'\right]\right\} \mathrm{d}s. \tag{2.21}$$

The equilibrium configurations of c make $\mathcal{F}$ stationary, that is, they make the first variation $\delta\mathcal{F}$ of $\mathcal{F}$ vanish identically. Since only the first-order variation $\boldsymbol{u}$ enters $\delta\mathcal{F}$, the equilibrium configurations for c, also in the presence of the constraint on the enclosed area, can easily be obtained with a slight extension of the method presented both in [17, 18]: these equations finally read as follows:

$$\begin{cases} \left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'' - \sigma\left(\lambda + \psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right) + \mu = 0 & \text{on} \quad c^* \\ [\![\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}]\!]\sigma_* + [\![\psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}]\!] - w = 0 & \text{in} \quad \mathcal{D}. \end{cases} \tag{2.22}$$

Here, λ and μ are Lagrange multipliers associated with $(2.20)_1$ and $(2.21)_1$, respectively. Moreover, for any function χ defined along the curve, the *jump* of χ across a detachment point is defined as

$$[\![\chi]\!] := (\chi)_{c_*} - (\chi)_{c^*} \tag{2.23}$$

where $(\chi)_{c_*}$ and $(\chi)_{c^*}$ are the limiting values of χ as the detachment point is approached from either the adhering or the free curve, respectively.

In [9] we discussed the stability of the equilibrium configurations of $\mathcal{F}_e$ with respect to a class of perturbations that did not displace the detachment points. Here, we explore precisely the role of these points in the stability of vesicles. As usual, our stability analysis relies on computing the second variation of $\mathcal{F}[c]$:

$$\delta^2\mathcal{F}(c) := \left.\frac{\mathrm{d}^2\mathcal{F}[c_\varepsilon]}{\mathrm{d}\varepsilon^2}\right|_{\varepsilon=0}.$$

For simplicity, we shall henceforth consider only perturbations around a single point of $\mathcal{D}$, say p_2. More precisely, if p_2 corresponds to the value $s = L_*$ of the arc-length on c, we consider fields $\boldsymbol{u}$ and $\boldsymbol{v}$ with support in the interval $[L_* - s_0, L_* + s_0]$ with s_0 sufficiently small.

By using (2.12) and (2.13), it is possible to see that

$$\delta^2\mathcal{F}(c) = \int_c \left\{ 2\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\left[(\boldsymbol{v}'\cdot\boldsymbol{\nu})' - \sigma(\boldsymbol{v}'\cdot\boldsymbol{t}) - \frac{\sigma}{2}(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2 - ((\boldsymbol{u}'\cdot\boldsymbol{t})(\boldsymbol{u}'\cdot\boldsymbol{\nu}))' \right] \right.$$
$$\left. + \frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}[(\boldsymbol{u}'\cdot\boldsymbol{\nu})' - \sigma(\boldsymbol{u}'\cdot\boldsymbol{t})]^2 + 2\psi\left[(\boldsymbol{v}'\cdot\boldsymbol{t}) + \frac{1}{2}(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2 \right] \right\} \mathrm{d}s$$
$$- 2w\int_{c_*}\left[(\boldsymbol{v}'\cdot\boldsymbol{t}) + \frac{1}{2}(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2 \right]\mathrm{d}s. \tag{2.24}$$

Under our simplifying assumptions, the last integral in (2.24) contributes a single boundary term, as can be seen by an integration by parts and using $(2.17)_2$:

$$\int_{c_*}\left[(\boldsymbol{v}'\cdot\boldsymbol{t}) + \frac{1}{2}(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2 \right]\mathrm{d}s = v_t(L_*).$$

A comment on the sign of the boundary terms is now appropriate. Since discontinuities at the detachment point p_2 are generally possible in the integrands, here integrations on c^* and c_* must be taken separately. Along the arc of c^* in support of both variations $\boldsymbol{u}$ and $\boldsymbol{v}$, s ranges in $[L_*, L_* + s_0]$, and so a boundary term arising at $s = L_*$ from integrations by parts acquires a negative sign. Contrariwise, along the arc of c_* in support of both variations, s ranges in $[L_* - s_0, L_*]$, and so a similar boundary term acquires a positive sign. Finally, at the end points $s = L_* \pm s_0$ both $\boldsymbol{u}$ and $\boldsymbol{v}$ vanish with their derivatives, and so no boundary term arises there.

By performing several integrations by parts, we can recast (2.24) as

$$\delta^2\mathcal{F}(c) = 2\int_{c_*\cup c^*}\left\{ \left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'' - \sigma\left(\psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right) \right] + v_\nu\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}[(\boldsymbol{u}'\cdot\boldsymbol{\nu})' - \sigma(\boldsymbol{u}'\cdot\boldsymbol{t})]^2 \right.$$
$$\left. + \left(\psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2 + 2\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'(\boldsymbol{u}'\cdot\boldsymbol{t})(\boldsymbol{u}'\cdot\boldsymbol{\nu}) \right\}\mathrm{d}s$$
$$+ 2\left\{ \left[\!\left[\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}(\boldsymbol{v}'\cdot\boldsymbol{\nu}) \right]\!\right] + \left[\!\left[\psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} \right]\!\right] v_t - wv_t \right.$$
$$\left. - \left[\!\left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)' \right]\!\right] v_\nu - \left[\!\left[\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} \right]\!\right](\boldsymbol{u}'\cdot\boldsymbol{t})(\boldsymbol{u}'\cdot\boldsymbol{\nu}) \right\}_{s=L_*} \tag{2.25}$$

where use has also been made of the following identity:

$$\left(\psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)' = -\sigma\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)' \tag{2.26}$$

which makes the sum of the terms in v_t vanish in the integrand of (2.25). Since $\boldsymbol{v}'\cdot\boldsymbol{\nu}$ is continuous at $s = L_*$, it can be estimated from its limit along c_*, which by $(2.17)_2$ and $(2.19)_2$ reads as

$$\boldsymbol{v}'\cdot\boldsymbol{\nu} = \sigma_* v_t + \tfrac{1}{2}\left[\left(\sigma u_t^2\right)'\right]_* \qquad \text{at} \quad s = L_*$$

where σ_* and $(\sigma')_*$ are the limiting values at $s = L_*$ of the curvature and its derivative along c_*. Likewise, by $(2.17)_1$ and $(2.19)_1$ we also have that

$$(\boldsymbol{u}'\cdot\boldsymbol{t})(\boldsymbol{u}'\cdot\boldsymbol{\nu}) = (\sigma u_t u_t')_* \qquad \text{at} \quad s = L_*.$$

Thus, by $(2.22)_2$, the boundary term in (2.25) can be rewritten as

$$2\left\{ \left[\!\left[\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} \right]\!\right]\sigma_* v_t + \left[\!\left[\psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} \right]\!\right] v_t - wv_t - \frac{1}{2}\left[\!\left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)' \right]\!\right]\sigma_* u_t^2 + \frac{1}{2}\left[\!\left[\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} \right]\!\right](\sigma')_* u_t^2 \right\}_{s=L_*}$$
$$= -\left\{ \left(\left[\!\left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)' \right]\!\right]\sigma_* - \left[\!\left[\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} \right]\!\right](\sigma')_* \right) u_t^2 \right\}_{s=L_*}. \tag{2.27}$$

Moreover, still by using (2.18) and (2.19), we can recast the integral along c^* in (2.25) as

$$\int_{c^*}\left\{\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}(\sigma' u_t + u_\nu'' + \sigma^2 u_\nu)^2 + \left(\lambda + \psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)(\sigma u_t + u_\nu')^2 - \mu\left[\sigma\left(u_t^2 + u_\nu^2\right)\right.\right.$$
$$\left.\left. + u_t u_\nu' - u_\nu u_t'\right] + 2\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'(\sigma u_t u_t' + u_t' u_\nu' - \sigma^2 u_t u_\nu - \sigma u_\nu u_\nu')\right\}\mathrm{d}s \tag{2.28}$$

where the equilibrium equation $(2.22)_1$ and both constraints $(2.20)_2$ and $(2.21)_2$ have been employed to show that

$$2\int_{c^*}\left\{\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'' - \sigma\left(\psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)\right\}v_\nu\,\mathrm{d}s$$
$$= \int_{c^*}\lambda\{(\sigma u_t + u_\nu')^2 - \mu\left[\sigma\left(u_t^2 + u_\nu^2\right) + u_t u_\nu' - u_\nu u_t'\right]\mathrm{d}s. \tag{2.29}$$

Equation (2.28) can be further simplified by resorting to the identity

$$\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)' = \left(\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\right)\sigma' \tag{2.30}$$

in the following equations:

$$\int_{c^*}\sigma'\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}u_t u_\nu''\,\mathrm{d}s = -\int_{c^*}\left\{\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'' u_t u_\nu' + \left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)' u_t' u_\nu'\right\}\mathrm{d}s - \left\{\left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)' u_t u_\nu'\right]^*\right\}_{s=L_*}$$

$$\int_{c^*}\sigma^2\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}u_\nu u_\nu''\,\mathrm{d}s = -\int_{c^*}\left[\left(\sigma^2\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\right)' u_\nu u_\nu' + \sigma^2\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}(u_\nu')^2\right]\mathrm{d}s$$

where the upper star in the boundary term means that it is computed as a limit along c^*, and use has been made of the fact that u_ν vanishes at every detachment point. Thus, by repeated integrations by parts, and by using $(2.22)_1$ and (2.26), we can give (2.28) the following form:

$$\int_{c^*}\left\{\left[\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}(\sigma')^2 + \sigma\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'' - \left(\sigma\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right)'\right]u_t^2 + \frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}(u_\nu'')^2\right.$$
$$+\left[\lambda + \psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} - 2\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\sigma^2\right](u_\nu')^2 + \left[\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\sigma^4 + \left(\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\sigma^2\right)''\right.$$
$$\left.\left. + \left(\sigma\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right)' - \mu\sigma\right]u_\nu^2\right\}\mathrm{d}s - \left\{\left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\left(2u_t u_\nu' + \sigma u_t^2\right)\right]^*\right\}_{s=L_*}. \tag{2.31}$$

By (2.30), the coefficient of u_t^2 in the above integrand vanishes identically. Moreover, by the continuity at $s = L_*$ of $\boldsymbol{u}'\cdot\boldsymbol{\nu}$, since u_ν vanishes identically along c_*, it follows from $(2.19)_1$ that

$$(u_\nu')^* = [\![\sigma]\!]u_t \qquad \text{at} \quad s = L_* \tag{2.32}$$

and so the boundary term in (2.31) can also be written as

$$-\left\{\left(2\left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right]^*[\![\sigma]\!] + \left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\sigma\right]^*\right)u_t^2\right\}_{s=L_*}. \tag{2.33}$$

By means of (2.17) the integral along c_* in equation (2.25) can be recast as

$$\int_{c_*}\left\{\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)''\sigma u_t^2 + \frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}(\sigma' u_t)^2 + 2\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\sigma u_t u_t'\right\}\mathrm{d}s. \tag{2.34}$$

A further integration by parts and use of (2.30) reduces (2.34) to a single boundary term:

$$\left\{\left[\sigma\left(\frac{\partial\psi}{\partial\sigma}\right)'\right]_* u_t^2\right\}_{s=L_*} \tag{2.35}$$

where the lower star reminds us that the limiting value is to be computed along c_*. Thus, putting together the integral in (2.31) and the boundary terms in (2.27), (2.33) and (2.35), we finally give (2.25) the following form:

$$\begin{aligned}\delta^2\mathcal{F}(c) = \int_{c^*}&\left\{\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}(u_\nu'')^2 + \left[\lambda+\psi-\sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}-2\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\sigma^2\right](u_\nu')^2\right.\\ &\left.+\left[\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\sigma^4+\left(\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\sigma^2\right)''+\left(\sigma\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right)'-\mu\sigma\right]u_\nu^2\right\}\mathrm{d}s\\ &+\left\{\left(\left[\!\left[\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right]\!\right](\sigma')_*-\left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right]^*[\![\sigma]\!]\right)u_t^2\right\}_{s=L_*}\end{aligned} \tag{2.36}$$

where further use has also been made of (2.23).

Equation (2.36) holds in a special class of equilibrium configurations for c: it has been obtained under some simplifying assumptions; in particular, $\mathcal{D}$ has been taken as composed of only two points and the perturbations of c have been localized around one of them. These assumptions do not limit in essence the validity of equation (2.36), which can indeed be easily extended to a more general class of equilibrium configurations. To this end, we remark that the integrand in (2.36) is invariant under reversal of the orientation of c, while the boundary term is not: an appropriate convention for the orientation of c must be introduced at all points of $\mathcal{D}$ to make any extension of (2.36) non-contradictory. The right convention is suggested by our derivation of (2.36) as follows: at every point $p_* \in \mathcal{D}$ the positive orientation of c is directed *away* from the substrate. Such an orientation is only valid locally at the points of $\mathcal{D}$ and cannot be extended to the whole curve c. In particular, according to this convention, the endpoints of a single arc of c_* are opposite oriented. The formula that generalizes (2.36) differs from it only in the boundary term, which is no longer one, but a sum of many:

$$\sum_{p_*\in\mathcal{D}}\left\{\left[\!\left[\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right]\!\right](\sigma')_*-\left(\left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right]^*[\![\sigma]\!]\right)u_t^2\right\}_{p_*} \tag{2.37}$$

where the above convention on the orientation of c enters in computing the derivatives relative to the arc-length.

When the curvature σ does not vanish along the equilibrium configuration of the free curve c^*, the integral in (2.36) can be given a much neater form, at the expense of the boundary terms in (2.37), which acquire an extra contribution. It is shown in appendix B that for the equilibrium configurations c of a vesicle where $\sigma \neq 0$ the second variation of the energy functional $\delta^2\mathcal{F}(c)$ can also be written as

$$\begin{aligned}\delta^2\mathcal{F}(c) = \int_{c^*}&\left\{\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\left(-u_\nu''+\frac{\sigma'}{\sigma}u_\nu'-\sigma^2u_\nu\right)^2-\mu\left(\sigma u_\nu^2-\frac{1}{\sigma}(u_\nu')^2\right)\right\}\mathrm{d}s\\ &+\sum_{p_*\in\mathcal{D}}\left\{\left(\left[\!\left[\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right]\!\right](\sigma')_*-\left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right]^*[\![\sigma]\!]-\left[\frac{1}{\sigma}\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right]^*[\![\sigma]\!]^2\right)u_t^2\right\}_{p_*}.\end{aligned} \tag{2.38}$$

Here, the integral coincides with that found in [9], where the detachment points were held fixed and μ was set equal to 0. In section 4, we shall build upon (2.38) in a particular case relevant for tubules.

In both forms (2.36) and (2.38), $\delta^2\mathcal{F}(c)$ is a quadratic functional of the first-order variation $\boldsymbol{u}$ subject to both conditions $(2.20)_1$ and $(2.21)_1$, while the Lagrange multipliers λ and μ are those computed on the given equilibrium configuration c by enforcing the constraints on the total length L of c and on the area A enclosed by c. It is worth noting that for a curve c not subject to any gliding condition on a fixed substrate our method of computing the second variation $\delta^2\mathcal{F}$, which resorts to both first- and second-order variations of c in (2.9), is completely equivalent to the standard method valid in the presence of isoperimetric constraints, which employs only the first-order variation $\boldsymbol{u}$ (see, for example, section 3.14 of [19]). The method introduced here, which eventually led us to a functional $\delta^2\mathcal{F}$ depending only on $\boldsymbol{u}$, is however necessary whenever a pointwise constraint is also present such as the one borne by adhesion. In this case, before evaporating from the final appearance of $\delta^2\mathcal{F}$, the second-order variation $\boldsymbol{v}$ introduces a wealth of boundary terms which are indeed the novelty of our result.

3. Integral identity

In the spirit of [15], to check the consistency of equation (2.25) we require the second variation $\delta^2\mathcal{F}(c)$ to be invariant under rotations in the plane of c, for all possible configurations of c that are free from adhesion. As a result, we obtain an integral identity that, for a quadratic free-energy density ψ, reproduces an identity derived in [16] by requiring the free-energy functional to be scale invariant.

By applying equation (2.25) to a curve c such that $c = c^*$ and using equations $(2.14)_2$ and $(2.16)_2$ combined with the equilibrium equation $(2.22)_1$, we arrive at

$$\delta^2\mathcal{F}(c) = \int_c \left\{ \lambda(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2 - \mu[(\boldsymbol{u}\cdot\boldsymbol{t})(\boldsymbol{u}'\cdot\boldsymbol{\nu}) - (\boldsymbol{u}\cdot\boldsymbol{\nu})(\boldsymbol{u}'\cdot\boldsymbol{t})] + \frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}[(\boldsymbol{u}'\cdot\boldsymbol{\nu})' - \sigma(\boldsymbol{u}'\cdot\boldsymbol{t})]^2 \right.$$
$$\left. + \left(\psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)(\boldsymbol{u}'\cdot\boldsymbol{\nu})^2 + 2\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'(\boldsymbol{u}\cdot\boldsymbol{t})(\boldsymbol{u}'\cdot\boldsymbol{\nu}) \right\} \mathrm{d}s. \tag{3.1}$$

This integral must vanish identically on all fields $\boldsymbol{u}_R$ representing a rotation:

$$\boldsymbol{u}_R = \boldsymbol{\omega} \times (p - o) \tag{3.2}$$

where $\boldsymbol{\omega} = \omega\boldsymbol{e}_z$ is an arbitrary vector orthogonal to the plane of c and o is an arbitrary point in this plane. It readily follows from (3.2) that

$$\boldsymbol{u}_R'\cdot\boldsymbol{t} = 0 \qquad \text{and} \qquad \boldsymbol{u}_R'\cdot\boldsymbol{\nu} = \omega. \tag{3.3}$$

By (3.3), $\delta^2\mathcal{F}_e(c)$ in (3.1) becomes

$$\delta^2\mathcal{F}(c) = -\omega^2\int_c \left\{ \left(\sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} - \psi\right) - \lambda - \mu(p-o)\cdot\boldsymbol{\nu} \right\} \mathrm{d}s \tag{3.4}$$

which, also by (2.8), vanishes for all ω, provided that

$$\int_c \left(\sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} - \psi\right)\mathrm{d}s - \lambda L - 2\mu A = 0 \tag{3.5}$$

where L and A are the prescribed values of the length of c and of the area enclosed by c, respectively. Since $\left(\sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} - \psi\right)$ is the Legendre transform of ψ, equation (3.5) has a transparent energetic interpretation that suggests to regard λ as the *tension* along c and μ as half the *pressure* inside it. The elastic energy plays no role in the identity (2.11) of [16], obtained for vesicles in three space dimensions because this energy is scale invariant, provided it is quadratic in the curvatures. By contrast, a quadratic functional fails to be scale invariant in two space dimensions: as a consequence, the free-energy density enters the integral identity (3.5) through its Legendre transform.

4. Susceptibility to fluctuations

Here we apply the main result of this paper to estimate the susceptibility to transverse fluctuations of an adhering tubule in a stable equilibrium configuration. Since we restrict attention to tubules, the area enclosed by the admissible curves c is not constrained and the corresponding Lagrange multiplier μ will be set equal to zero. In particular, for a specific choice of the energy density ψ, we compute the least value of $\delta^2\mathcal{F}(c)$ for a prescribed equilibrium configuration and within a given class of perturbations: as is well known (see, for example, section 111 of [20]), the minimum of $\delta^2\mathcal{F}(c)$ corresponds to the maximum susceptibility to fluctuations of the assigned curve c. The equilibrium configurations considered here are locally stable, so that the minimum attained by $\delta^2\mathcal{F}(c)$ is strictly positive. Our main aim is to illuminate the role played by the curvature of the adhesive substrate in determining the tubule susceptibility to a selected class of fluctuations: this will ultimately measure to what extent a geometric feature of the substrate can conspire with the adhesion potential, which is a material property of the substrate, to enhance or depress the ability of the substrate to hold the tubule in a given equilibrium configuration. Our study is partially limited by the two-dimensional nature of our model: we cannot consider fluctuations of the tubule corresponding to longitudinal modes suggesting a kind of *peristaltic* deformation, we can only envisage deformations of the planar cross-section c of the tubule, which are the same all along the extension of the tubule.

We take for the elastic-energy density ψ the following quadratic function of the curvature σ:

$$\psi(\sigma) = \frac{\kappa}{2}\sigma^2 \tag{4.1}$$

where the constant $\kappa > 0$ is a constitutive parameter, called the *bending rigidity* of the membrane constituting the tubule. Here we consider as an adhesive substrate either a *plane*, or a cylindrical *groove*, or a cylindrical *bump* (see figure 2): in all these cases, $\sigma' \equiv 0$ along the transverse cross-section to which the curve c adheres. Inserting (4.1) into equation $(2.22)_2$ leads us to the equilibrium condition

$$[\![\sigma]\!] = -\sqrt{\frac{2w}{\kappa}} \tag{4.2}$$

valid at every detachment point. For simplicity, as in section 2, we take the set $\mathcal{D}$ of the detachment points as $\{p_1, p_2\}$ and we choose p_1 as the origin of the arc-length s along c, so that $s = L_*$ at p_2, where L_* is the length of the adhered curve c_*. We consider perturbations $\boldsymbol{u}$ that vanish at p_1 and are assigned a given value u_0 to the tangential component u_t at p_2. We further assume that the equilibrium configuration of the free curve c^* is such that $\sigma \neq 0$. By (2.4), this assumption allows us to employ equivalently s and ϑ to parametrize the curve c^*: one variable can be changed into the other, letting $s = L_*$ correspond to $\vartheta = \vartheta^*$ and setting conventionally $\vartheta = 0$ for $s = \frac{L_*}{2}$. Moreover, by the chain-rule,

$$\sigma' = \dot{\sigma}\sigma \tag{4.3}$$

where the dot denotes differentiation with respect to ϑ and the same symbol σ has been used for both functions in the variables s and ϑ. We shall adopt this old-fashioned habit also for other functions below: the appropriate argument will explicitly be indicated whenever confusion could otherwise arise. Under these assumptions, equation (2.38) becomes

$$\delta^2\mathcal{F}(c) = \kappa\int_{c^*}\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\left(-u_\nu'' + \frac{\sigma'}{\sigma}u_\nu' - \sigma^2 u_\nu\right)^2\mathrm{d}s + \left\{\sqrt{\frac{2w}{\kappa}}\left(1 - \frac{1}{\sigma^*}\sqrt{\frac{2w}{\kappa}}\right)(\sigma')^* u_0^2\right\}_{s=L_*}. \tag{4.4}$$

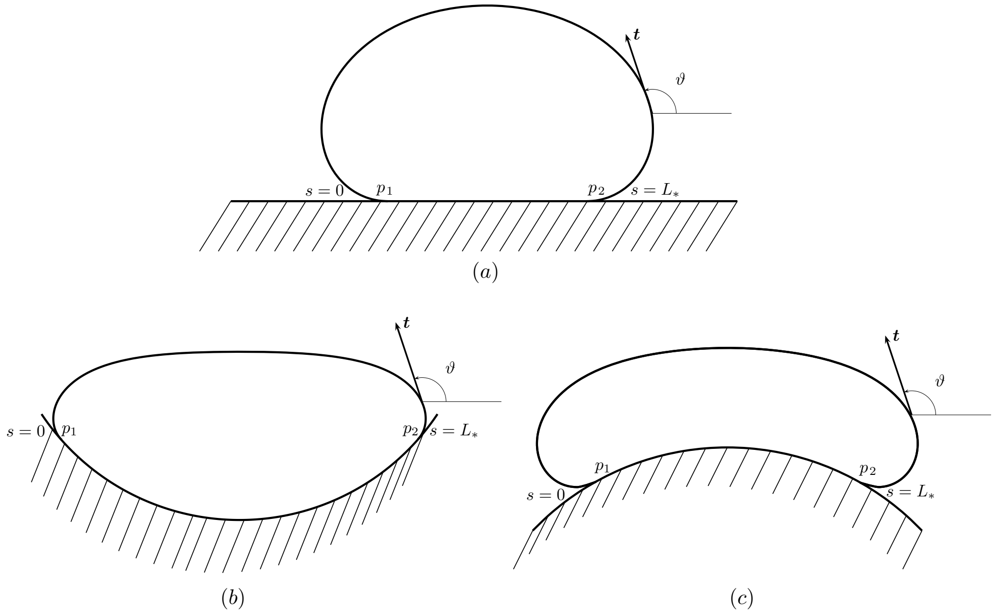

Figure 2. Illustration of the different situations envisaged here: the tubule, of which only the cross-section c is shown here, either adheres to a plane (*a*), or to a cylindrical groove (*b*), or to a cylindrical bump (*c*). The length L of c is the same in all three cases and the equilibrium configurations are all symmetric.

It was proved in [18] that for a tubule adhering to a flat substrate the curvature of the free curve c^* is

$$\sigma(\vartheta) = \sqrt{\frac{2w}{\kappa}}\sqrt{\nu + (1-\nu)\cos\vartheta} = \sigma^*\sqrt{\nu + (1-\nu)\cos\vartheta} \tag{4.5}$$

where the Lagrange multiplier ν must be chosen so as to satisfy the constraint

$$\frac{L}{2} = \int_0^\pi \frac{1-\cos\vartheta}{\sigma(\vartheta)}\,\mathrm{d}\vartheta$$

and $\sigma^* := \sqrt{\frac{2w}{\kappa}}$ is the curvature of c^* at the detachment point, where $\vartheta^* = 0$. As shown in [18], a unique equilibrium solution exists if and only if $L \geqslant 2\pi\sqrt{\frac{\kappa}{2w}}$. It follows from both (4.3) and (4.5) that

$$(\sigma')^* = \sigma(0)\dot{\sigma}(0) = 0$$

and so the boundary term in (4.4) vanishes and $\delta^2\mathcal{F}(c)$ is clearly non-negative. When the tubule adheres either to a cylindrical groove or to a cylindrical bump, the curvature σ_* of the substrate is correspondingly either $+\frac{1}{R}$ or $-\frac{1}{R}$. Adhesion of tubules to a groove was studied in [17], where it was proved that a unique equilibrium solution exists, provided that the length L of c ranges in a suitable bounded interval. Since in this case $\sigma^* > \sqrt{\frac{2w}{\kappa}}$ and $(\sigma')^* < 0$, the boundary terms in (4.4) are negative. Similarly, it was proved in [21] that for tubules adhering to a cylindrical bump there is a unique equilibrium configuration for which $(\sigma')^* > 0$, and so the boundary term in (4.4) is still negative because, by (4.2), $\sqrt{\frac{2w}{\kappa}} - \frac{1}{\sigma^*} < 0$. These remarks indicate that the local stability of the unique equilibrium configuration for tubules adhering to both grooves and bumps must follow from a prevailing positive contribution to $\delta^2\mathcal{F}(c)$ of the integral in (4.4): the analysis that follows will substantiate this claim.

To shorten the notation, we set $u := u_\nu$ and also change in u the variable s into ϑ, so that, together with (4.3), we have

$$u' = \sigma\dot{u}. \tag{4.6}$$

Similarly,

$$u'' = \sigma\dot{\sigma}\dot{u} + \sigma^2\ddot{u}$$

so that the integral in (4.4) reads as

$$\kappa F^{(2)}(\sigma)[u] := \kappa\int_0^{\vartheta_0}\sigma^3(\ddot{u}+u)^2\,\mathrm{d}\vartheta \tag{4.7}$$

where the origin of ϑ has been shifted for convenience to ϑ^* and ϑ_0 is the angle spanned by ϑ all along c^*, from p_2 to p_1. Since in our class of admissible fluctuations u_0 is fixed, the minimum of $\delta^2\mathcal{F}(c)$ in (4.4) corresponds to the minimum of $F^{(2)}$ subject to the constraint $(2.20)_1$, which here reads as

$$\int_0^{\vartheta_0} u\,\mathrm{d}\vartheta = 0. \tag{4.8}$$

Thus we seek the extremals of the functional

$$F_\lambda^{(2)}(\sigma)[u] := \int_0^{\vartheta_0}\sigma^3(\ddot{u}+u)^2\,\mathrm{d}\vartheta + 2\lambda\int_0^{\vartheta_0} u\,\mathrm{d}\vartheta \tag{4.9}$$

where λ is a Lagrange multiplier to be determined so as to satisfy (4.8). Moreover, it follows from (2.32) and (4.6) that the boundary conditions appropriate for u in (4.9) are

$$u(0) = u(\vartheta_0) = 0 \qquad \dot{u}(0) = a \qquad \dot{u}(\vartheta_0) = 0 \tag{4.10}$$

where we have set

$$a := \frac{[\![\sigma]\!]}{\sigma^*}u_0. \tag{4.11}$$

The Euler–Lagrange equation for $F_\lambda^{(2)}$ is then easily obtained:

$$[\sigma^3(\ddot{u}+u)]^{\cdot\cdot} + \sigma^3(\ddot{u}+u) + \lambda = 0.$$

By setting

$$q := \sigma^3(\ddot{u}+u)$$

we arrive at

$$q(\vartheta) = A\cos\vartheta + B\sin\vartheta - \lambda$$

where A and B are integration constants, and so u satisfies the differential equation

$$\ddot{u} + u = \frac{A\cos\vartheta + B\sin\vartheta - \lambda}{\sigma^3} =: f(\vartheta) \tag{4.12}$$

which is solved by the following function (see e.g. pp 14–15 of Bender and Orszag [22]):

$$u(\vartheta) = -\cos\vartheta\int_0^{\vartheta} f(t)\sin t\,\mathrm{d}t + \sin\vartheta\int_0^{\vartheta} f(t)\cos t\,\mathrm{d}t + C\cos\vartheta + D\sin\vartheta \tag{4.13}$$

where C and D are other integration constants. Requiring this function to obey the boundary conditions in (4.10), we obtain the equations

$$\begin{aligned} C &= 0 \qquad D\sin\vartheta_0 - \cos\vartheta_0\int_0^{\vartheta_0} f(t)\sin t\,\mathrm{d}t + \sin\vartheta_0\int_0^{\vartheta_0} f(t)\cos t\,\mathrm{d}t = 0 \\ D &= a \qquad D\cos\vartheta_0 + \sin\vartheta_0\int_0^{\vartheta_0} f(t)\sin t\,\mathrm{d}t + \cos\vartheta_0\int_0^{\vartheta_0} f(t)\cos t\,\mathrm{d}t = 0. \end{aligned} \tag{4.14}$$

Also enforcing (4.8), after integrations by parts, we arrive at

$$D(1-\cos\vartheta_0) - \sin\vartheta_0\int_0^{\vartheta_0} f(t)\sin t\,\mathrm{d}t + \int_0^{\vartheta_0} f(t)\,\mathrm{d}t - \cos\vartheta_0\int_0^{\vartheta_0} f(t)\cos t\,\mathrm{d}t = 0. \tag{4.15}$$

By using $(4.14)_3$, equations $(4.14)_{2,4}$ and (4.15) become a linear, non-homogeneous system for A, B and λ:

$$\begin{aligned} &A(I_4\cos\vartheta_0 - I_6\sin\vartheta_0) + B(I_5\cos\vartheta_0 - I_4\sin\vartheta_0) + \lambda(I_1\sin\vartheta_0 - I_2\cos\vartheta_0) = a\sin\vartheta_0 \\ &A(I_4\sin\vartheta_0 + I_6\cos\vartheta_0) + B(I_5\sin\vartheta_0 + I_4\cos\vartheta_0) - \lambda(I_1\cos\vartheta_0 + I_2\sin\vartheta_0) = -a\cos\vartheta_0 \\ &A(I_4\sin\vartheta_0 + I_6\cos\vartheta_0 - I_1) + B(I_5\sin\vartheta_0 + I_4\cos\vartheta_0 - I_2) \\ &\qquad + \lambda(I_3 - I_1\cos\vartheta_0 - I_2\sin\vartheta_0) = a(1-\cos\vartheta_0) \end{aligned}$$

where the coefficients

$$\begin{aligned} I_1 &:= \int_0^{\vartheta_0}\frac{\cos\vartheta}{\sigma^3(\vartheta)}\,\mathrm{d}\vartheta \qquad & I_2 &:= \int_0^{\vartheta_0}\frac{\sin\vartheta}{\sigma^3(\vartheta)}\,\mathrm{d}\vartheta \qquad & I_3 &:= \int_0^{\vartheta_0}\frac{1}{\sigma^3(\vartheta)}\,\mathrm{d}\vartheta \\ I_4 &:= \int_0^{\vartheta_0}\frac{\sin\vartheta\cos\vartheta}{\sigma^3(\vartheta)}\,\mathrm{d}\vartheta \qquad & I_5 &:= \int_0^{\vartheta_0}\frac{\sin^2\vartheta}{\sigma^3(\vartheta)}\,\mathrm{d}\vartheta \qquad & I_6 &:= \int_0^{\vartheta_0}\frac{\cos^2\vartheta}{\sigma^3(\vartheta)}\,\mathrm{d}\vartheta \end{aligned}$$

must be computed on a specific equilibrium solution for σ. Once A, B and λ are obtained, by (4.7) and (4.12), $F^{(2)}$ results from

$$F^{(2)}(\sigma)[u] = \int_0^{\vartheta_0}\frac{(A\cos\vartheta + B\sin\vartheta - \lambda)^2}{\sigma^3}\,\mathrm{d}\vartheta$$

or else, from

$$F^{(2)}(\sigma)[u] = I_6A^2 + I_5B^2 + I_3\lambda^2 + 2I_4AB - 2I_1\lambda A - 2I_2\lambda B. \tag{4.16}$$

By rescaling σ to σ^* and u to L, so that both $\tilde{\sigma} := \frac{\sigma}{\sigma^*}$ and $\tilde{u} := \frac{u}{L}$ are dimensionless, and defining the dimensionless parameters

$$\xi := L\sqrt{\frac{2w}{\kappa}} \qquad \text{and} \qquad \varrho := \frac{R}{L}$$

the former of which measures the adhesion potential of the substrate relative to the stiffness of the membrane, while the latter measures the curvature of the substrate, we finally give the second variation in (4.4) the following form:

$$\delta^2\mathcal{F}[c] = \frac{\kappa}{L}\left(\frac{[\![\sigma]\!]}{\sigma^*}\tilde{u}_0\right)^2\left(\xi \pm \frac{1}{\varrho}\right)^3\left[F^{(2)}(\tilde{\sigma})[\tilde{u}] + \frac{\nu\sin\vartheta^*}{2\xi\varrho}\right] \tag{4.17}$$

where either the plus or the minus sign should be taken, as to whether the substrate is a bump or a groove. In equation (4.17), $\tilde{u}_0 := u_0/L$ and ν is a Lagrange multiplier depending on the equilibrium solution $\tilde{\sigma}$ in a manner similar to that recorded in (4.5). It should be noted that the minimum of $F^{(2)}$ depends in an rather intricate manner on both ξ and ϱ, essentially

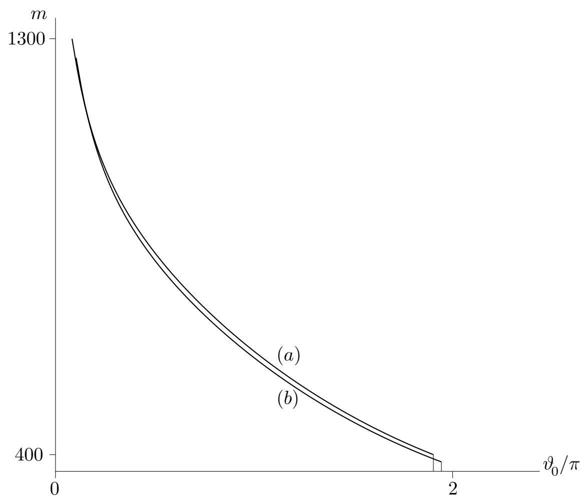

Figure 3. Graphs of the normalized minimum m of the second variation $\delta^2\mathcal{F}(c)$ against the angular amplitude ϑ_0 of the fluctuations. The tubule adheres to grooves of different radii R, but the qualitative features of the graph are independent of R. Parameters: (a) $\xi = 1, \varrho = 55, \vartheta^* = 0.066$; (b) $\xi = 1, \varrho = 110, \vartheta^* = 0.033$. In these graphs ϑ_0 ranges over the interval $]0, 2(\pi - \vartheta^*)]$, which has a different extension in the two cases.

through the equilibrium configuration of the tubule. Employing the explicit solutions found in [17, 18] for the three different substrates envisaged here, that is, a plane, a groove and a bump, we evaluated numerically the expression in (4.17) with the aid of (4.16). We illustrate below the outcomes of our computations.

$\delta^2\mathcal{F}(c)$ turned out to be *positive* in all cases we computed, regardless of the substrate, thus granting stability to the given equilibrium configurations against the fluctuations considered here. The minimum value of $\delta^2\mathcal{F}(c)$ always corresponds to the maximum admissible value of ϑ_0, that is, 2π for the flat substrate, $2(\pi - \vartheta^*)$ for the groove and $2(\pi + \vartheta^*)$ for the bump. Figure 3 shows how the minimum of $\delta^2\mathcal{F}(c)$ depends on ϑ_0, for given ξ, when the tubule adheres to grooves of different curvatures; similar curves were also obtained for bumps, but they are not reproduced here because they would be almost indistinguishable from those in figure 3. Precisely, the graphs in figure 3 represent the function

$$m(\vartheta_0) := \frac{\min_{\tilde{u}} \delta^2\mathcal{F}(c)}{\frac{\kappa}{L}\left(\frac{[\![\sigma]\!]}{\sigma^*}\tilde{u}_0\right)^2}.$$

Clearly, the fluctuations with maximum extension make adhered tubules most susceptible to detachment in all geometric settings considered here. Moreover, the effect of the substrate curvature on the susceptibility to fluctuations of an adhered tubule is illuminated by figure 4, where the minimum of m is plotted against ϱ, again for given ξ, for grooves, bumps and a flat substrate. Clearly, the maximum susceptibility grows while the substrate changes from a groove into a bump.

We close this section by confirming with an asymptotic analysis the appearance of the graphs in figure 3, which suggests that m diverges as $\vartheta_0 \to 0$. When ϑ_0 is very small, we are indeed perturbing a short arc of c^* near the detachment point p_2, and so the curvature σ of c^* can be approximated by the value σ^* it takes at p_2. Thus, $F^{(2)}(\sigma)$ can be estimated by $F^{(2)}(\sigma^*)$ and the same analysis performed above for $F^{(2)}(\sigma)$ now delivers an explicit analytic

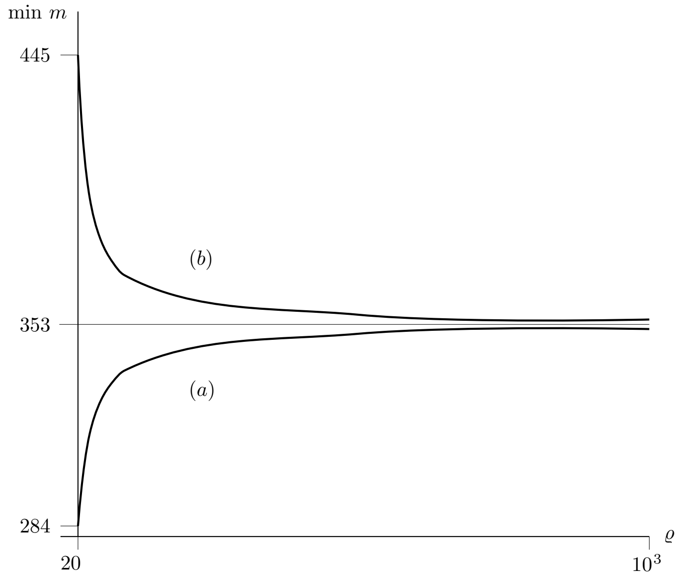

Figure 4. The minimum of m in ϑ_0 measures the maximum susceptibility of the tubule to fluctuations. Here it is plotted against ϱ for different substrates and a fixed value of ξ. Curve (a) applies to a bump, and curve (b) applies to a groove. When ϱ increases, and so the substrate curvature decreases, the maximum susceptibility approaches one and the same value regardless of whether the substrate is a groove or a bump: this limit coincides with the maximum susceptibility of a tubule adhering on a flat substrate. The lower bound $\varrho = 20$ is the minimum value of ϱ that ensures, for the selected value of ξ, the existence of equilibrium configurations adhering to a groove, to a bump and to a flat wall.

formula for the minimum of $F^{(2)}(\sigma^*)$, which exhibits the same divergence as m:

$$\begin{aligned}\frac{\min_{\tilde{u}} F^{(2)}(\sigma^*)[\tilde{u}]}{\frac{\kappa}{L}\left(\frac{[\![\sigma]\!]}{\sigma^*}\tilde{u}_0\right)^2} &= \frac{9 - 6\vartheta_0^2 - 16\cos\vartheta_0 + 7\cos 2\vartheta_0 + 8\vartheta_0\sin\vartheta_0 + 2\vartheta_0\sin 2\vartheta_0}{2(\sin\vartheta_0 - \vartheta_0)\left(\vartheta_0^2 - 4 + 4\cos\vartheta_0 + \vartheta_0\sin\vartheta_0\right)} \\ &\approx \frac{9}{\vartheta_0} + O(1).\end{aligned}$$

5. Conclusion

Within a two-dimensional model, we gave a general formula for the second variation of the energy functional of a vesicle adhering to a rigid substrate, arbitrarily curved. Arriving at this formula required developing a method able to translate into a mathematical language the particular detachment mechanism we envisaged: The classical method for computing the second variation, which is applicable when isoperimetric constraints are enforced is inapplicable here, since a pointwise constraint is present. As was to be expected, a crucial role is played here by detachment points, that is, the points where the curve representing the vesicle comes in contact with the substrate: the new terms in the formula for the second variation arise precisely there. We applied our formula to compute the susceptibility to detachment of an adhered equilibrium configuration of a tubule within a specific class of fluctuations. In particular, we illuminated the role of the substrate curvature in the response of the adhered tubule to detaching fluctuations: qualitatively, these are more efficient when the tubule adheres to an extroverted bump than when it adheres to an introverted groove. Such a difference in susceptibility is quantitatively measured by the minimum of the second variation of the energy functional.

Appendix A. Gliding conditions

In this appendix, we prove the equations in (2.17) that express the condition that a planar curve c deformed as in (2.9) *glides* over a fixed curve in the same plane containing c. At least locally, the fixed curve can be represented by

$$f(p) = 0$$

for a suitable function f that we shall assume of class C^2. There, the unit normal vector $\boldsymbol{\nu}$ to c can also be written as

$$\boldsymbol{\nu} = \frac{\nabla f}{|\nabla f|}. \tag{A.1}$$

The gliding condition requires that

$$f(p + \varepsilon \boldsymbol{u} + \varepsilon^2 \boldsymbol{v}) = o(\varepsilon^2)$$

which amounts to the equation

$$\varepsilon \nabla f \cdot \boldsymbol{u} + \frac{\varepsilon^2}{2}[\boldsymbol{u} \cdot (\nabla^2 f)\boldsymbol{u} + 2\nabla f \cdot \boldsymbol{v}] = 0.$$

Requiring this equation to be satisfied at both orders in ε, we arrive at

$$\nabla f \cdot \boldsymbol{u} = 0 \qquad \text{and} \qquad \boldsymbol{u} \cdot (\nabla^2 f)\boldsymbol{u} + 2\nabla f \cdot \boldsymbol{v} = 0. \tag{A.2}$$

By using (A.1) we then compute

$$\nabla \boldsymbol{\nu} = \frac{1}{|\nabla f|}\nabla^2 f - \nabla f \otimes \frac{1}{|\nabla f|^2}\nabla(|\nabla f|)$$

and since

$$\nabla(|\nabla f|) = (\nabla^2 f)\boldsymbol{\nu}$$

we conclude that

$$\nabla \boldsymbol{\nu} = \frac{1}{|\nabla f|}(\mathbf{I} - \boldsymbol{\nu} \otimes \boldsymbol{\nu})\nabla^2 f = \frac{1}{|\nabla f|}(\boldsymbol{t} \otimes \boldsymbol{t})\nabla^2 f$$

whence, also by $(2.3)_2$, it follows that

$$\boldsymbol{t} \cdot (\nabla \boldsymbol{\nu})\boldsymbol{t} = \boldsymbol{t} \cdot \boldsymbol{\nu}' = -\sigma = \frac{1}{|\nabla f|}\boldsymbol{t} \cdot (\nabla^2 f)\boldsymbol{t}. \tag{A.3}$$

Now, by (A.1), $(\mathrm{A.2})_1$ is the same as $(2.17)_1$, and it implies that $\boldsymbol{u} = u_t \boldsymbol{t}$. Inserting this equation into $(\mathrm{A.2})_2$ and using both (A.1) and (A.3), we then prove $(2.17)_2$.

Appendix B. Alternative form of $\delta^2 \mathcal{F}$

In [9] we studied the stability of the planar cross-section c of tubules, to which the constraint on the enclosed area does not apply, under the assumption that in the unperturbed equilibrium configurations of c the curvature σ vanishes nowhere. We proved that whenever the perturbations of c are confined within the free curve c^*, the second variation of the elastic energy $\mathcal{F}_e$ is given by

$$\int_{c^*} \frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\left(-u_\nu'' + \frac{\sigma'}{\sigma}u_\nu' - \sigma^2 u_\nu\right)^2 \mathrm{d}s \tag{B.1}$$

whence it follows immediately that every equilibrium configuration of c is locally stable, provided that ψ is a convex function of σ.

Here we start from (B.1) to find an alternative form of $\delta^2\mathcal{F}$ valid when the perturbations of c also involve the adhering curve c_*, still under the assumption that $\sigma \neq 0$. We make below the same simplifying assumptions as in section 2: we take $\mathcal{D} = \{p_1, p_2\}$ and we perturb c selectively around p_2, where $s = L_*$.

By expanding the square in the integrand of (B.1) and performing several integrations by parts, the integral in (B.1) can be rewritten as

$$\int_{c^*} \left\{ \frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\left((u_\nu'')^2 + \left(\frac{\sigma'}{\sigma}\right)^2 (u_\nu')^2 + \sigma^4 u_\nu^2\right) + \left(\frac{\sigma'}{\sigma}\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\right)'(u_\nu')^2 + 2\sigma^2\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}(u_\nu')^2 \right.$$
$$\left. - 2\left[\left(\sigma^2\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\right)' + \sigma\sigma'\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\right]u_\nu u_\nu' \right\}\mathrm{d}s + \left\{\left[\frac{\sigma'}{\sigma}\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}(u_\nu')^2\right]^*\right\}_{s=L_*}.$$

Use of (2.30) and further integrations by parts reduce this expression to

$$\int_{c^*} \left\{ \frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}(u_\nu'')^2 + \left[\frac{1}{\sigma}\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'' - 2\sigma^2\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\right](u_\nu')^2 + \left[\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\sigma^4 + \left(\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\sigma^2\right)'' \right.\right.$$
$$\left.\left. + \left(\sigma\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right)'\right]u_\nu^2\right\}\mathrm{d}s + \left\{\left[\frac{1}{\sigma}\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'(u_\nu')^2\right]^*\right\}_{s=L_*}. \tag{B.2}$$

Since, by $(2.22)_1$,

$$\frac{1}{\sigma}\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'' = \lambda + \psi - \sigma\frac{\mathrm{d}\psi}{\mathrm{d}\sigma} - \mu\frac{1}{\sigma}$$

comparing (2.36) and the expression in (B.2), and recalling that the latter equals the integral in (B.1), we easily arrive at

$$\delta^2\mathcal{F}(c) = \int_{c^*}\left\{\frac{\mathrm{d}^2\psi}{\mathrm{d}\sigma^2}\left(-u_\nu'' + \frac{\sigma'}{\sigma}u_\nu' - \sigma^2 u_\nu\right)^2 - \mu\left(\sigma u_\nu^2 - \frac{1}{\sigma}(u_\nu')\right)^2\right\}\mathrm{d}s$$
$$+ \left\{\left(\left[\!\left[\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right]\!\right](\sigma')_* - \left[\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right]^*[\![\sigma]\!] - \left[\frac{1}{\sigma}\left(\frac{\mathrm{d}\psi}{\mathrm{d}\sigma}\right)'\right]^*[\![\sigma]\!]^2\right)u_t^2\right\}_{s=L_*} \tag{B.3}$$

where use of (2.32) has also been made. The extension of (B.3) to the general formula (2.38) then follows by applying the same convention on the orientation of c introduced at the end of section 2.

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