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Research Paper

Disease System Analysis: Basic Disease Progression Models in Degenerative Disease

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Purpose. To describe the disease status of degenerative diseases (i.e., type 2 diabetes mellitus, Parkinson's disease) as function of disease process and treatment effects, a family of disease progression models is introduced.
Methods. Disease progression is described using a progression rate (R_{dp}) acting on the synthesis or elimination parameters of the indirect response model. Symptomatic effects act as disease-dependent or -independent effects on the synthesis or elimination parameters. Protective drug effects act as disease-dependent or -independent effects on R_{dp}.
Results. Simulations with the ten disease models show distinctly different signature profiles of treatment effects on disease status. Symptomatic effects result in improvement of disease status with a subsequent deterioration. Treatment cessation results in a disease status equal to the situation where treatment had not been applied. Protective effects result in a lasting reduction, or even reversal, of the disease progression rate and the resulting disease status during the treatment period. After cessation of treatment the natural disease course will continue from the disease status at that point.
Conclusion. Disease system analysis constitutes a scientific basis for the distinction between symptomatic *versus* protective drug effects in relation to specific disease processes as well as the identification of the exposure-response relationship during the time-course of disease.

KEY WORDS: biomarkers; clinical endpoints; disease progression analysis; disease system analysis; indirect response model.

INTRODUCTION

Over the past two decades, pharmacokinetic–pharmacodynamic (PK/PD) models have been developed for characterization of the time course of drug effects. Specifically, PK/PD models relate drug exposure to effects on biomarkers for efficacy and safety, and/or clinical responses (1,2). The additional incorporation of population (mixed-effects) characteristics accounts for the inherent intra- and interindividual variability of a structural PK/PD relationship.

Mechanistic PK/PD models contain specific expressions to describe the pharmacokinetics, the mechanism of action of the drug, and one or more physiological processes. A specific feature of these models is the distinction between drug- and system-specific parameters. Thereby, the values of the latter parameters are limited to physiological ranges and even inaccessible pharmacodynamic steps can be estimated (2,3). Within the context of PK/PD modeling, the family of indirect physiological response (IPR) models constitutes a useful basis for the development of mechanism-based PK/PD models, which can be extended to describe transduction processes, complex time-dependent physiological mechanisms, and disease processes (2–5). Characterization of the effect of a drug in such a system involves the interfacing with a pharmacokinetic model and the incorporation of receptor theory to describe and predict the equilibrium drug concentration–effect relationship (6–12). In this manner, the first fully mechanism-based PK/PD model, based on interfacing of a receptor model and a transduction model, was recently proposed (3).

In conventional PK/PD analyses, the values of the model parameters that determine the status of a biological system in the absence of a drug are (kept) invariable with time, and physiology is generally considered constant at baseline. For progressive, chronic diseases, this is not a realistic description because biological functions may deteriorate over the time course of the treatment period.

Therefore, disease progression analysis has been proposed where the influence of a drug effect on the change in disease status over time is characterized (13–17). Disease progression analysis constitutes an extension of traditional PK/PD analysis, as time-dependent changes in the dynamics of the biological system of diseased subjects are accounted for as an additional level. This is important when drug treatment is specifically intended to modify disease processes and disease progression.

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Disease Progression Models

Chan and Holford were among the first to present clinical pharmacology in terms of natural disease progression and drug action (13). Disease progression can be analyzed at different levels of the pathophysiology (Fig. 1). The initial disturbance in a biological system relates to the complex interaction between genetic, transcription-, and receptor-mediated events at a molecular level (18). This results in changes in the functioning of cells and/or tissues, which comprise the second level of effects. At both levels, relevant biomarkers can offer an improved insight in the dynamics of the biological system and the latter are anticipated to predict the clinical response faster or with increased precision (3,19–24). Finally, symptoms—as expressed by organ function and/or clinical rating scales—describe the ultimate clinical response on a third level. Eventually, effects at these three levels converge in the long-term clinical outcome in terms of morbidity and mortality.

In principle, the drug effect on the disease process can be analyzed at each of the aforementioned levels. Chan and Holford reviewed disease progression models based on clinical endpoints for diseases such as Parkinson's disease, Alzheimer's disease, respiratory disease, diabetic nephropathy, and osteoporosis (13). In these models, as well as in several other examples (14–16, 25–29), the disease status or symptoms of the disease are described as a direct function of treatment, without characterization of the underlying biological system. Such a descriptive approach is useful when only clinical endpoints are the available measurements reflecting disease and drug action. However, if the underlying biological system is (partly) known and biological markers for specific aspects of the disease process in this system have been identified, a more comprehensive and mechanistic description of disease progression is feasible. Identification of disease progression and drug action on such a basis will be referred to as disease system analysis. Similar to mechanistic PK/PD analysis, a relationship can ultimately be established between the time course of the drug concentration on one hand, and both the disease process and the resulting disease status on the other.

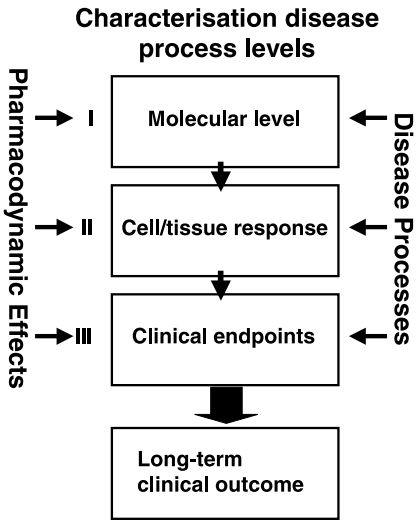

Fig. 1. Domain of disease system analysis. The levels present the stages of disease progression. Here, a biological function within the homeostatic system is disturbed in level I or II, resulting in a disease process, which can be reflected in clinical endpoints. The three disease levels specifically present the combined outcome of, on the one hand, disease processes and, on the other, the pharmacodynamic effects. The disease over time can be described at each of these levels, depending on the information available. Ultimately, these three levels converge in long-term clinical outcomes. The roman numbers indicate the specific levels of a disease system in this domain (I → III, in a mechanistically decreasing order of complexity) where disease progression is assessable.

Classification of Treatment Effects in Disease System Analysis

Disease progression analysis includes both a qualitative and a quantitative characterization of the drug effect on the disease status over time. Qualitatively, drug treatment can result in clinical benefit in two ways:

(1) Symptomatic treatment effect—an improvement in the disease status without altering the process of disease progression.

(2) Protective treatment effect—modification of the underlying process of disease, resulting in a change in the time course of the disease severity.

In theory, protective drug effects can reduce, halt, or even reverse the disease process, whereas symptomatic treatments can only reduce symptom severity (13).

Assessment of Drug Efficacy

Traditionally, clinical trials assess the efficacy of drugs in the patient population by comparing the disease status at the start of treatment and at one or more time-points during or after the treatment period. Typically, classical analysis of variance between groups at fixed time-points quantifies the differences between treatments. Within this paradigm, a last observation carried forward (LOCF) approach is often applied to account for dropout of study subjects and/or missing measurement visits (30–32). However, this introduces uncertainty and bias in the outcome of the analysis (32,33). Furthermore, for sparsely sampled data with relatively irregular numbers and timings of measurements, this leads to a substantial loss of statistical power. Finally, the traditional statistical approaches do not provide a basis for extrapolation and prediction, as the underlying trajectory of the disease is being ignored. Application of disease progression analysis, based on nonlinear regression and mixed-effects analysis, may overcome these issues. In addition to a more accurate and precise quantification of treatment effects, based on drug-specific target sites within the system, the disease process is expressed in a mathematical structure, and a qualitative evaluation of the drug effect in terms of a distinction between a protective *vs.* a symptomatic effect is feasible.

Inherently, a qualitative evaluation of treatment effects requires that a disease progression model must distinguish between drug-specific properties and disease-specific properties. Because physiological parameters are unique to the biological system, they are independent of the compound tested (3,34). This also enables differentiation between short- and long-term treatment effects, based on pertinent biomarkers, before they are observed in clinical endpoints. Ultimately, a combined analysis of the disease system based on biomarkers

in relation to clinical endpoints or clinical outcome (morbidity, mortality) allows the comparison of drug effects.

Aim

In this paper, a family of basic disease progression models is proposed, in which the status of degenerative diseases over time is described via indirect physiologic response models. The observed disease status stems from time-dependent changes in the underlying process of a biological system. Specifically, we propose a theoretical framework for application of disease system analysis in progressive degenerative diseases caused by an ongoing disturbance of homeostasis. This disturbance of homeostasis results from a declining process controlling the biological function, which corresponds to the degenerative nature of the disease.

MATERIALS AND METHODS

Homeostatic System. Disease progression is defined as a change in disease status over time. This implies that in the situation of a healthy homeostatic system no change in any of the biological system parameters exists. Using an indirect physiological response model, this results in time-invariant biological system parameters (2,4,5). In such a case, the primary differential equations describing the homeostasis of the biological process are:

$$\frac{dS}{dt} = k_{in} - k_{out}S \tag{1}$$

with

$$\frac{dk_{in}}{dt} = 0 \qquad \frac{dk_{out}}{dt} = 0 \tag{2}$$

where the change dS/dt in the measured status (S) of a biological system over time is controlled by a constant zero-order synthesis process (k_{in}) and a constant first-order elimination process (k_{out}).

Disease Progression. In case of chronic degenerative diseases, homeostasis is disturbed by a time-dependent change

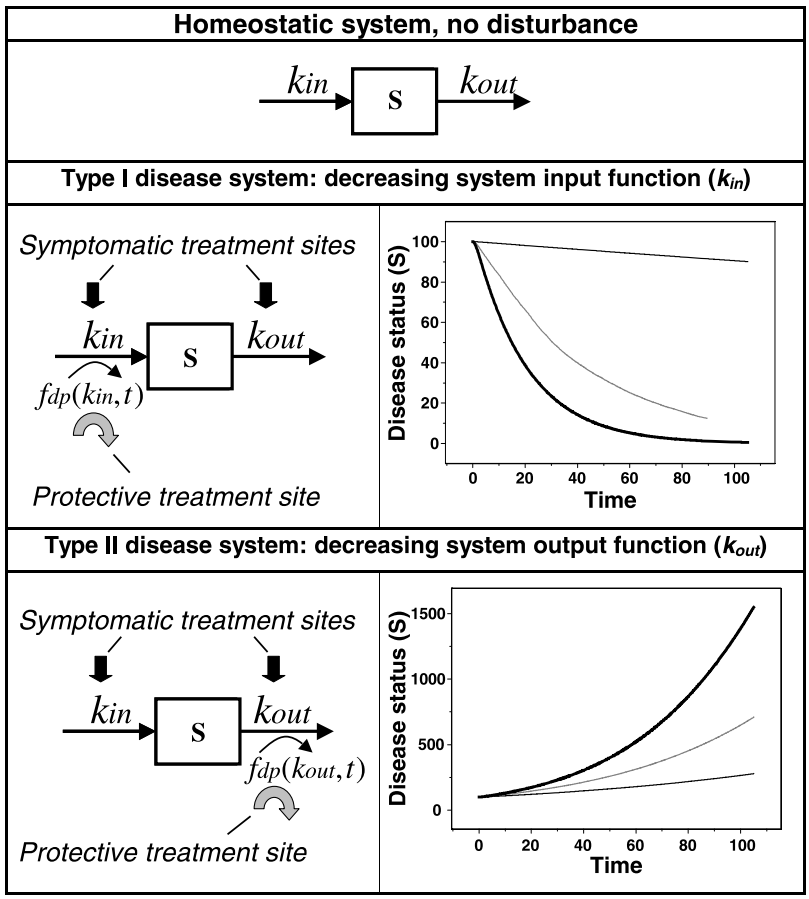

Fig. 2. Models of disease progression resulting from a decline in either the synthesis or elimination process controlling the homeostatic system. For each type of disease progression model, three rates of disease progression are presented, visualizing possible progression curvatures (Type I (R_{dp}); [0.001,0.05], Type II (R_{dp}); [0.01,0.03]). Black block arrows represent target sites for symptomatic effects. Grey curved block arrows represent target sites for protective effects. Top: Indirect physiological response (IPR) model without disturbance in homeostasis. Middle: Disturbance in homeostasis due to an exponentially decreasing synthesis process (Type I). Bottom: Disturbance in homeostasis due to an exponentially decreasing elimination process (Type II).

Table I. Description of Type I (decreasing k_{in}) and Type II (decreasing k_{out}) Disease Systems with Two Classes of Treatment Effects: Symptomatic and Protective

Disease system		Treatment effect on			
		Synthesis k_{in} (I)		Elimination k_{out} (II)	
Nomenclature	Parameter	Protective	Symptomatic	Protective	Symptomatic
Type I	k_{in}: decreased synthesis	↑ change (dk_{in}/dt)	↑ status (k_{in})[a]	[b]	↓ status (k_{out})[c]
Type II	k_{out}: decreased elimination	[b]	↓ status (k_{in})[c]	↑ change (dk_{out}/dt)	↑ status (k_{out})[a]

[a] The status of a disease-affected system parameter can be altered by a disease-independent symptomatic treatment effect, changing the parameter with a constant offset, or by a disease-dependent symptomatic treatment effect, shifting the progressively declining status of the disease-affected parameter proportionally.
[b] Not possible in these disease systems, since the parameter is unaffected by disease and a protective effect influences the change of the parameter over time.
[c] The status of a disease-unaffected system parameter can be altered by a symptomatic treatment effect, changing parameter with a constant offset.

in either the process of synthesis or elimination, resulting in an ongoing deterioration of the status of the system. Here, the situation of a degenerative disease is considered, in which there is a decrease in either the synthesis (disease system Type I) or the elimination (disease system Type II).

In Fig. 2, the natural course of disease progression and potential target sites of treatment are presented. A degenerative process affecting synthesis can be described by substituting the following:

$$\frac{dk_{in}}{dt} = f_{dp}(k_{in}, t) \tag{3}$$

in Eq. (1), where, the change in synthesis (k_{in}) over time is a function of disease state (f_{dp}). In case of a first-order process, this becomes:

$$f_{dp}(k_{in}, t) = -R_{dp}k_{in} \tag{4}$$

where R_{dp} is the first-order disease progression rate constant. Similarly, a degenerative process affecting elimination can be described as:

$$\frac{dk_{out}}{dt} = f_{dp}(k_{out}, t) \tag{5}$$

with

$$f_{dp}(k_{out}, t) = -R_{dp}k_{out} \tag{6}$$

where the change in elimination (k_{out}) over time is a function of disease state (f_{dp}). In principle, several functions can be applied to describe the disease progression. However, within the context of this paper, we constrain the function for disease progression to first-order self-limiting functions.

Therapeutic Intervention. Table I presents the possible disease systems in degenerative disease with the various treatment effects considered within the context of this paper. Therapeutic interventions on the disease process are divided into symptomatic and protective. Table II presents the proposed nomenclature for the various treatment effects within the disease systems.

Symptomatic Effect. An improvement in disease status without changing the (underlying) process of natural disease progression characterizes a symptomatic relief (13). This can be achieved through two different types of effect. The first type of symptomatic effect is disease-independent. This is achieved by the incorporation of an additive term to the status of a system parameter describing the synthesis or the elimination process (Table II, models $I.S_i.I \mid I.S_i.II \mid II.S_i.I \mid II.S_i.II$):

$$\frac{dS}{dt} = \{k_{in}(t) + f_s(D)\} - \{k_{out}(t) + f_s(D)\}S \tag{7}$$

Table II. Nomenclature of Various Disease Systems

Disease system	Treatment effect on			
	Synthesis k_{in} (I)		Elimination k_{out} (II)	
Nomenclature	Protective	Symptomatic	Protective	Symptomatic
Type I	$I.P_d$ $I.P_i$	$I.S_i.I$ $I.S_d.I$	–	$I.S_i.II$
Type II	–	$II.S_i.I$	$II.P_i$ $II.P_d$	$II.S_i.II$ $II.S_d.II$

Symptomatic treatment effects are denoted as *S*, protective treatment efects as *P*. A treatment effect can be either disease-dependent ($_d$) or -independent ($_i$). The first roman number presents the type of disease system, in which the disease progression is either on k_{in} (I) or k_{out} (II). The second roman number presents the target-site of action, which can be either on k_{in} (I) or k_{out} (II). The second roman number is redundant in case of a protective treatment effect, as it can only affect a parameter affected by disease.

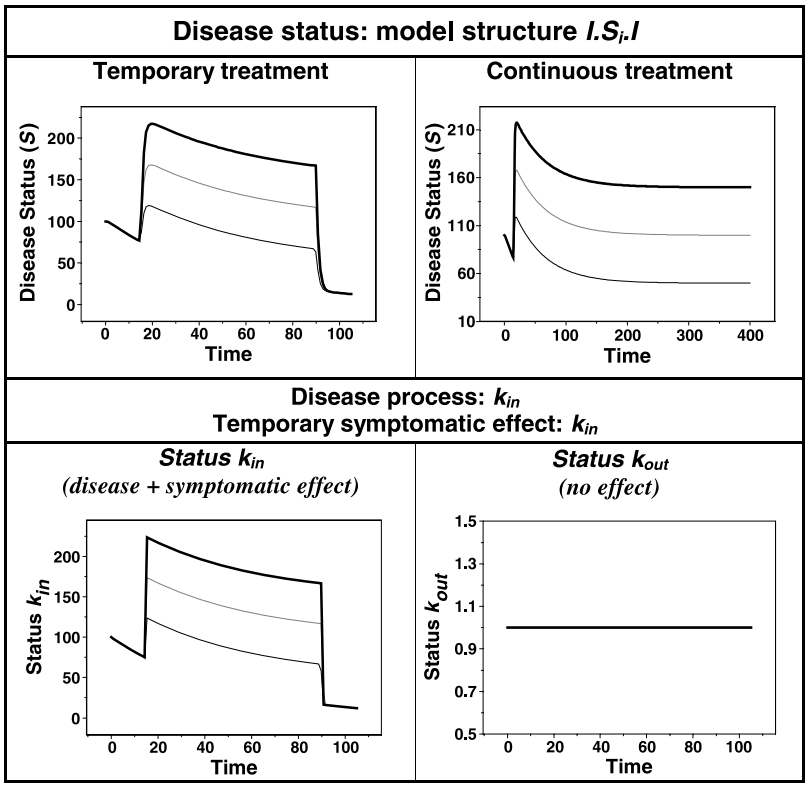

Fig. 3. Time course of the disease status resulting from a decreasing value of synthesis (k_{in}) with a disease-independent symptomatic effect on the input parameter: $I.S_i.I$. Three different direct effect levels are simulated: small (—), intermediate (—) and high (—). Top: Time course of the disease status with (left) and without (right) treatment cessation. Bottom left: Time course of value of k_{in} before, during, and after symptomatic treatment. Bottom right: Time course of value of k_{out}.

where either the synthesis process (k_{in}) or the elimination process (k_{out}) controlling the measured status (S) is affected by a time-dependent change [Eqs. (3) or (5)]. Here, the drug effect is a function of the exposure in terms of dose or concentration ($f_s(D)$). The second type of symptomatic effect is disease-dependent, which is incorporated in the model as a multiplicative term to the status of the affected synthesis or elimination process (Table II, models $I.S_d.I \mid II.S_d.II$):

$$\frac{dS}{dt} = \{k_{in}(t)f_s(D)\} - \{k_{out}(t)f_s(D)\}S \qquad (8)$$

where the drug effect ($f_s(D)$) proportionally modulates the status of parameter that is affected by a time-dependent change [Eq. (3) or (5)].

Protective Effect. An improvement in disease status resulting from modification of the degenerative process, which causes the natural disease progression, characterizes a protective effect (13). This is reflected by an alteration of the disease progression rate constant, followed by a change in the disease status over time. Here, a distinction is made between the alteration in the rate of change of an underlying disease process and the observed change in disease status. A pertinent feature of this model is that the mechanism of the delay in change of disease status for protective effects differs from a symptomatic effect.

Two kinds of protective treatment effects must be distinguished. The first is a disease-independent effect, where the capacity of a biological function is restored by addition of capacity, independent of the rate of progression (Table II, models $I.P_i \mid II.P_i$). The second is a disease-dependent effect, and reflects the situation where the disease progression rate constant is altered proportionally (Table II, models $I.P_d \mid II.P_d$). Protective treatment effects are always incorporated on the underlying parameter that determines the course of disease progression, as an additive term for disease-independent modification:

$$\frac{d(k_{in}, k_{out})}{dt} = f_{dp}(k_{in}, k_{out}, t) + f_p(D) \qquad (9)$$

and as a multiplicative term for disease-dependent modification:

$$\frac{d(k_{in}, k_{out})}{dt} = f_{dp}(k_{in}, k_{out}, t)f_p(D) \qquad (10)$$

The protective treatment effect ($f_p(D)$) modulates the parameter characterizing the disease progression [Eq. (3) or (5)] as a function of exposure in terms of dose or concentration.

Simulation. The properties of the various disease systems described above were evaluated by simulation, using Berkeley Madonna™ version 8.0.1 (Macey and Oster, University of

California, Berkeley). The simulations were performed with the following arbitrary parameter values: k_{in}, 100; k_{out}, 1; R_{dp}, 0.02; S (baseline disease status), 100. The symptomatic drug effects ($f_s(D)$) were simulated with the following arbitrary parameter values, presenting the small to high range for each disease system: I.S_i.I, [50,150]; I.S_i.II, [−0.1,−0.7]; II.S_i.I, [−10,−60]; II.S_i.II [0.1,0.6]; I.S_d.I [1.5,3]; II.S_d.II, [1.1,1.6]. The protective drug effects ($f_p(D)$) were simulated with the following arbitrary parameter values, presenting the small to high range for each disease system: I.P_i [1,3]; II.P_i [0.01,0.03]; I.P_d [0.25,−0.25]; II.P_d [0.25,−0.25]. The simulated data were processed using S-PLUS for Windows (version 6.2 Professional, release 1, Insightful Corp., Seattle, WA, USA).

RESULTS

The present approach for the analysis of progressive Type I and Type II degenerative diseases considers a first-order decay in either the process of synthesis or elimination controlling the biological system. Without treatment effects, the process of a declining synthesis (Type I degenerative disease) results in an asymptotic decrease of the disease status over time. A decreasing elimination process (Type II degenerative disease) results in an exponential increase of the disease status (Fig. 2).

The interactions between the disease process, the disease status, and the mechanism of treatment are considered as dynamic systems, which are described by sets of differential equations.

All responses are characterized by an immediate onset and offset of the drug effect. This immediate response enables a distinction between the interaction of the two main disease types and the treatment effect.

Symptomatic Effect. For symptomatic effects, drugs may influence the status of a system parameter by a constant offset, resulting in a disease-independent symptomatic effect [Eq. (7)]. This can be either on the parameter that is affected by the disease process (I.S_i.I, II.S_i.II), or through a compensation of the unaffected parameter (I.S_i.II, II.S_i.I). A symptomatic effect can also be achieved by changing the status of the disease-affected parameter proportionally, which results in a disease-dependent symptomatic effect [I.S_d.I, II.S_d.II, Eq. (8)].

At the start of treatment, symptomatic effects result in an improvement in the observed disease status, which originates from a shift in the status of an underlying process. Figures 3–6 show the influence of symptomatic effects on the time course of the disease status in Type I and II disease systems. The time course of the change in the underlying process controlling the observed disease status in a Type I disease system are illustrated in Figs. 3–5. At the level of the

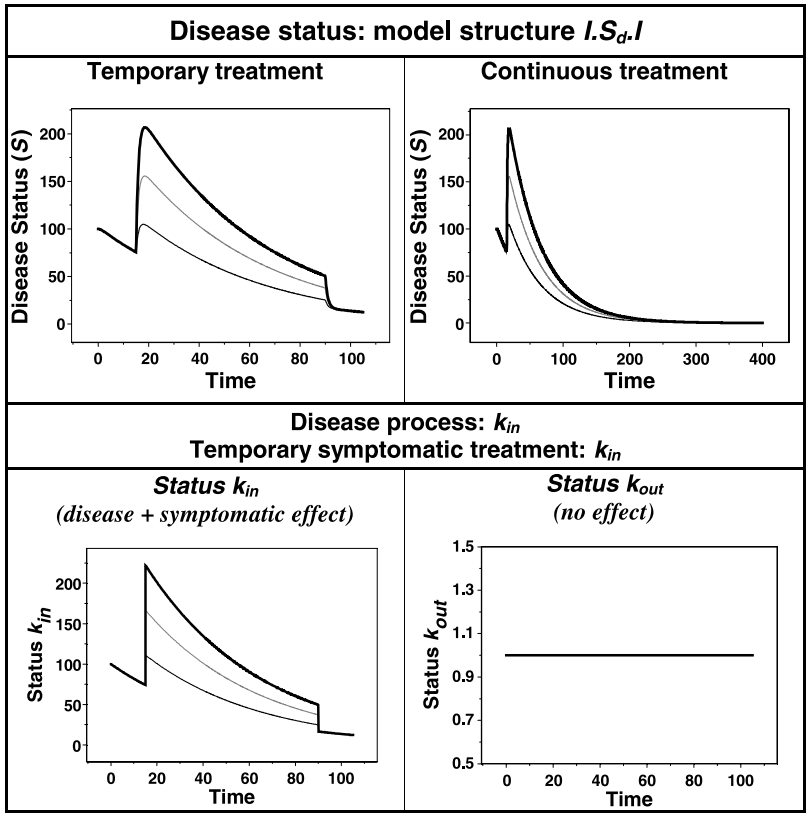

Fig. 4. Time course of the disease status resulting from a decreasing value of synthesis (k_{in}) with a disease-dependent symptomatic effect on the input parameter: I.S_d.I. Three different direct effect levels are simulated: small (—), intermediate (═) and high (▬). Top: Time course of the disease status with (left) and without (right) treatment cessation. Bottom left: Time course of the value of k_{in} before, during, and after symptomatic treatment. Bottom right: Time course of the value of k_{out}.

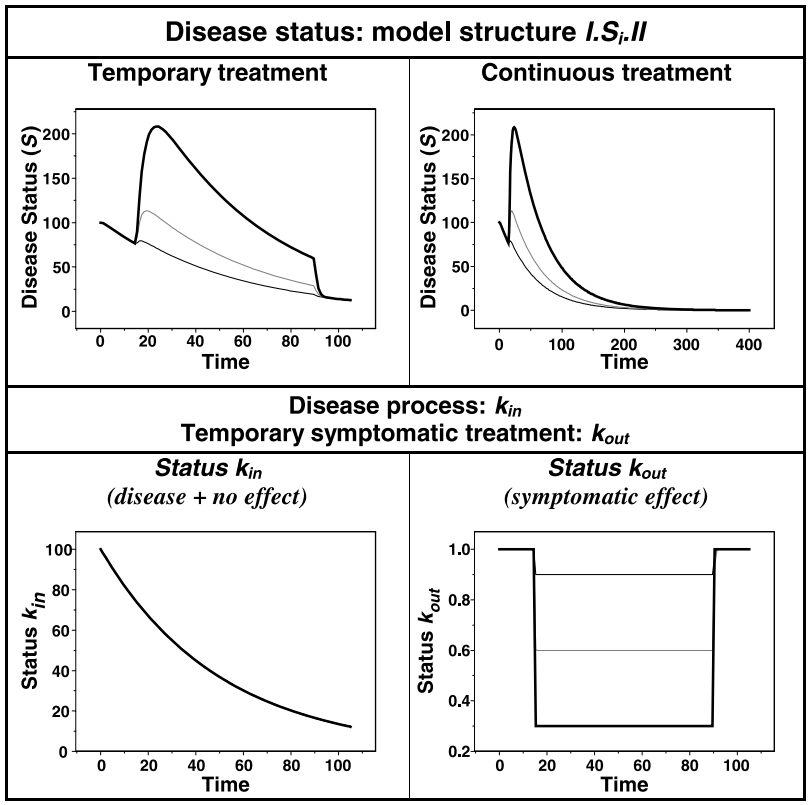

Fig. 5. Time course of the disease status resulting from a decreasing value of synthesis (k_{in}) with a disease-independent symptomatic effect on the output parameter: $I.S_i.II$. Three different direct effect levels are simulated: small (—), intermediate (—) and high (—). Top panel: Time course of the disease status with (left) and without (right) treatment cessation. Bottom left: Time course of the value of k_{in}. Bottom right: Time course of the value of k_{out} before, during, and after symptomatic treatment.

synthesis and elimination processes, the direct drug effect is initially proportional to the treatment intensity. However, time course of the effects in the resulting disease status differs. When the direct drug effect is on the process of synthesis, the immediate effect manifests itself proportionally to the treatment intensity [Figs. 3, 4, and 6 (bottom panel)]. In contrast, when the effect is on the process of elimination, the resulting immediate effect on the disease status is disproportional [Figs. 5 and 6 (top and middle panel)]. Specifically, for model structure $I.S_i.II$, a more than proportional improvement, and for $II.S_i.II$ and $II.S_d.II$, a less than proportional improvement is observed.

After the initial improvement, all symptomatic effects display an ongoing deterioration in the disease status, analogous to the transient nature of such treatment effects. This typical transient nature depends on the type of disease system and the target site of the symptomatic effect. Three basic profiles in the time courses of the underlying processes can be distinguished: (1) a progressive decline in the status of a process, at the rate of the natural disease progression when the drug effect is additive to a progressively declining parameter ($I.S_i.I$, $II.S_i.II$, Fig. 3); (2) a progressive decline in the status of a process, eventually approximating the rate of natural disease progression, as the drug effect is proportional to a progressively declining parameter ($I.S_d.I$, $II.S_d.II$, Fig. 4); and (3) a constant shift in the status of a process unaffected by disease progression ($I.S_i.II$, $II.S_i.I$, Fig. 5). These profiles correspond to disease-independent and disease-dependent effects on the disease-affected parameter and disease-independent effects on the disease-unaffected parameter, respectively.

A pertinent feature of model structures $I.S_i.I$, $II.S_i.II$ is the drug effect on the status of a process controlling the biological system that compensates for the disease progression. On treatment continuation, this leads to a new homeostasis as the drug effect is independent of the rate of disease progression. The other four remaining model structures do not result in a new homeostasis. For model structures $I.S_d.I$, $II.S_d.II$, the treatment effect is proportional to a progressively declining parameter and for model structures $I.S_i.II$, $II.S_i.I$ the disease is modified by changing the status of the disease-unaffected parameter, such that a new homeostasis cannot be attained. The observed disease status remains dominated by the disease progression.

Finally, on cessation of treatment the disease status returns to the natural disease status that would have been attained without treatment, which is characteristic for all symptomatic treatment effects (Figs. 3–6, left panels).

Protective Effect. For protective effects, drugs influence the disease process by an effect on the rate of change of the disease affected system parameter. This results in a direct change of the disease status over time, without an initial immediate improvement as observed with symptomatic effects. A disease-independent protective effect results from restoration of a biological function as an additive effect, independent of the rate of progression [$I.P_i$, $II.P_i$; Eq. (9)]. By

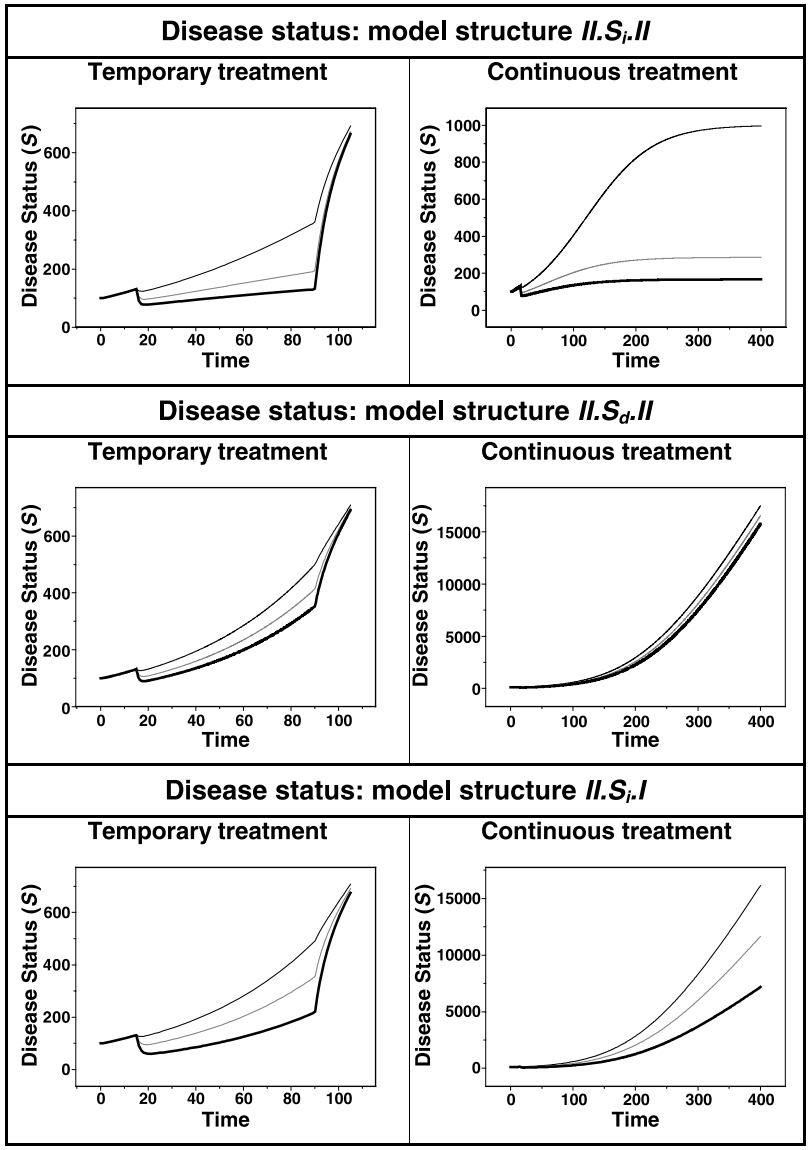

Fig. 6. Time course of the disease status resulting from a decreasing value of elimination (k_{out}) with a (1) disease-independent symptomatic effect on the output parameter: II.S_i.II (top), (2) disease-dependent symptomatic effect on the output parameter: II.S_d.II (middle), (3) disease-independent symptomatic effect on the input parameter: II.S_i.I (bottom). For each disease system, three different direct effect levels are simulated: small (—), intermediate (—) and high (—). The time course of the disease status with (left) and without (right) treatment cessation is presented.

changing the status of the disease-affected parameter in a proportional manner, a disease-dependent protective effect is obtained [I.P_d, II.P_d; Eq. (10)].

Figures 7 and 8 present both types of protective effects. Both effects can either reduce, halt, or even reverse rate of change of the disease status. However, a disease-independent effect always results in a new homeostasis of the disease status, depending on the magnitude of the effect on the biological function. A disease-dependent protective effect only results in a new homeostasis if it completely counteracts the disease progression rate parameter. Termination of a protective treatment effect results in a continuation of the natural disease course from the disease status at that point.

DISCUSSION

Outline Disease System Analysis

The currently proposed classification of disease progression analysis provides a scientific basis for investigating complex disease systems. A differentiation is made between the drug effect on the disease process and the resulting disease status over time. The present method can be considered a mechanistic approach as it takes into consideration the drug effect on the disease system underlying the change in clinical endpoints. This constitutes a scientific basis for identification of the mechanism of a drug effect on a

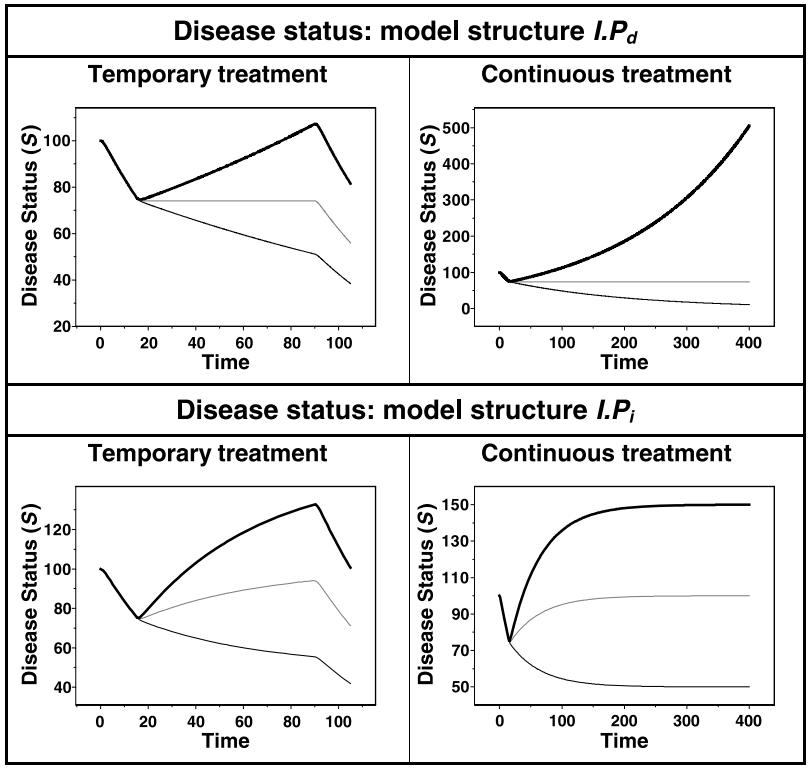

Fig. 7. Time course of the disease status resulting from a decreasing value of synthesis (k_{in}) with a (1) disease-dependent protective effect on the synthesis parameter: $I.P_d$ (top), (2) disease-independent protective effect on the synthesis parameter: $I.P_i$ (bottom). For each disease system, three different direct effect levels are simulated: small (—), intermediate (—) and high (—). The time course of the disease status with (left) and without (right) treatment cessation is presented.

disease process (specifically the distinction between a symptomatic and a protective effect) as well as identification of the exposure–response relationship.

Furthermore, it also constitutes a basis for extrapolation and prediction of drug effects on disease progression.

The basis of the proposed family of disease progression models is that progressive diseases result from a disturbance of a dynamic biological system. Clearly, this is a reduction of the complex of biological interactions within all physiological systems. Such a reduction is typical for all pharmacodynamic modeling. It involves a selection of endpoints that are both relevant and quantifiable either directly or indirectly (3,9,10,35). Besides the distinction between disease process and disease status over time, the approach also provides consistent definitions for the mode and implicit site of action of the drug treatment effects. In this way, a structural basis for the distinction between various symptomatic and protective drug treatment effects is proposed.

Illustration Disease System Analyses

The various treatment effects, both symptomatic and protective, are classified as being either disease-dependent or disease-independent. An example of a disease-independent symptomatic effect ($I.S_i.I$) is the effect of directly acting dopamine receptor agonists in the treatment of Parkinson's disease (36–39). A (theoretical) example of a disease-dependent symptomatic effect is stimulation of the release of dopamine from existing neurons, without altering the progressive degeneration of such neurons ($I.S_d.I$) (39–42). Inhibition of the elimination rate of endogenous dopamine would be another example ($I.S_i.II$) (39,40,42). An example of a disease-independent protective drug effect would be a treatment with growth factor, which promotes the generation of new dopamine releasing neurons, unaffected by disease progression ($I.P_i$) (39,40). A disease-dependent protective effect would be a reduction in the rate of decline of dopamine releasing neurons ($I.P_d$) (39,40).

Another example of a disease-dependent drug effect is the treatment of type 2 diabetes mellitus, where sulphonylurea (e.g., gliclazide) enhances the release of insulin, a response which, in turn, depends on the declining function of the β-cell (43). Within this context, treatment with insulin can be viewed as a disease-independent effect. The treatment of osteoporosis with bisphosphonates could also be considered as disease-independent as they interfere with the functioning of osteoclasts (44–46).

Perspective Disease System Analysis

A pertinent feature of the proposed classification of disease progression models is the distinction between different types of "symptomatic" drug treatment effects (13).

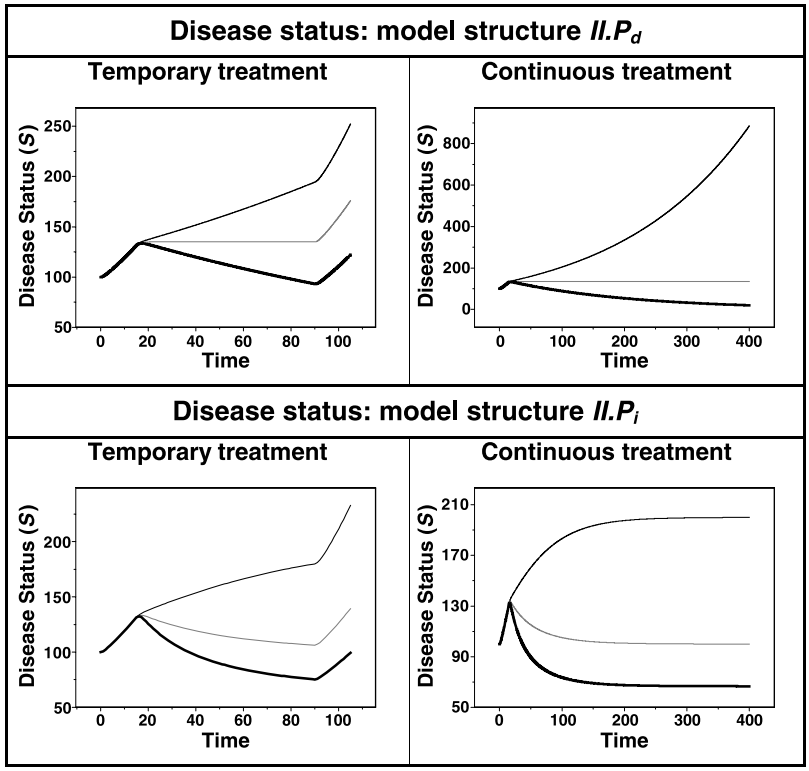

Fig. 8. Time course of the disease status resulting from a decreasing value of elimination (k_{out}) with a (1) disease-dependent protective effect on the elimination parameter: $II.P_d$ (top), (2) disease-independent protective effect on the elimination parameter: $II.P_i$ (bottom). For each disease system, three different direct effect levels are simulated: small (—), intermediate (—) and high (—). The time course of the disease status with (left) and without (right) treatment cessation is presented.

Specifically, in previously proposed descriptive disease progression models, a symptomatic effect is used to describe a delay in the disease state without alteration of the rate of progression, with ultimately a return to the original disease state. However, for a disease where the structure of the underlying system is known, various symptomatic drug treatment options exist, which do not necessarily result in a return to the original disease state, but are still symptomatic. This is illustrated in disease systems $I.S_i.I$ and $II.S_i.II$, where upon continuation of the treatment, a new homeostasis is reached (Figs. 3 and 6). When solely interpreted on an observational basis, this seems to be a protective effect, but from a mechanistic point of view it is a symptomatic effect. Simulations based on the proposed mechanistic model structures show that a symptomatic treatment effect results in a change in disease status during the treatment that is dependent on the type, duration, and the intensity of treatment. In addition to reaching a new homeostasis, this can either result in an accelerated or delayed return to the disease status at the start of treatment. Thus, the term "symptomatic" denotes more than a delay in the disease status profile. Depending on various factors, symptomatic treatment effects can result in a more beneficial outcome than a protective treatment effect. For instance, a symptomatic effect results in an initial improvement in disease status, which cannot be reached by a protective effect that slows down or halts disease progression, because it merely induces a direct effect on the rate of change in the disease status at that time-point, without directly improving the disease status.

Extensions to Disease System Analyses

The proposed mechanism-based disease models were specifically designed as basic models describing degenerative disorders on measurements of a single biomarker, with a decrease in either synthesis or elimination. For more complex homeostatic control mechanisms, when a multitude of biomarkers is required to characterize the disease process, the disease systems can be readily extended to represent a cascade of compartments. The process leading to the disturbed homeostasis can then be incorporated at different sites in the cascade, resulting in different disease profiles. A theoretical example of such an extension is a system in which the synthesizing or eliminating functions of the disease system itself are regulated by production and loss functions (Fig. 9). When these latter functions are influenced by a degenerative process, this would result in a different overall biomarker response.

An example of a population-based cascading disease model was recently presented for analysis of various therapeutic interventions in type 2 diabetes mellitus (47–49). Here, an (insulin-)fasting plasma glucose–HbA_{1c} system was modeled with various treatment target sites that are typical for each drug. This can be considered as an extended disease

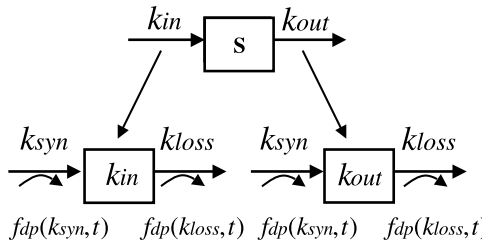

Fig. 9. Extended model of disease progression, where a combination of indirect response models is used to describe the disease system. The disturbance in the homeostasis of a biological system is modeled by describing a decrease over time of either the synthesizing (k_{syn}), or eliminating (k_{loss}) process controlling the synthesis (k_{in}), or elimination (k_{out}) of the homeostatic system.

system in which multiple biomarkers are required for a comprehensive description of the underlying changes in pathophysiology. In the diabetes example, each biomarker shows a typical time-scale of treatment response. The most rapid response is observed for insulin (hours to days), followed by a response in FPG (days to weeks), and finally by a response in HbA_{1c} (weeks to months). The existence of different time-scales within a disease system may allow for the prediction of long-term efficacy on the basis of short-term biomarker responses. The proposed disease systems can be extended with complexities such as nonstationary or time-dependent baselines, systems with tolerance development and counterregulatory and feedback mechanisms (50–52). In addition, the relation between the drug effect and the disease system can either be direct or indirect, and be linear or nonlinear, resulting in different disease status profiles. The proposed disease systems were based on a direct linear exposure–response relationship to delineate a clear distinction between the interaction of the two main disease types and the treatment effect.

The current analysis emphasizes on the theoretical aspects of such disease systems, presenting the specific properties and signature profiles of the examined disease progression models. However, statistical issues will play a substantial role when this concept is applied. These aspects, including parameter identifiability, discrimination between treatment effects, and disease progression, will give rise to practical issues, which are considered out of the scope of the current analysis.

Application in Clinical Trials

One of the goals in disease progression analysis is the differentiation between disease- and drug-specific parameters and the extrapolation of the behavior of a disease system beyond trial duration. These goals are more likely to be achieved when a more qualitative analysis of drug efficacy is performed including the trajectory of disease, in addition to the traditional methods that are often quantitative in nature (48).

An additional field of application for disease system analysis is the comparison of the long-term effects between drugs that act through different sites and modes of action within the disease system. Thus, during the process of drug development, specific therapeutic targets can be pursued and optimal treatment regimens can be identified, for example in the case of combination therapies (short- and long-term efficacy) that are applied in the treatment of HIV, diabetes, and cancer.

In summary, a set of basic disease model systems were specified with accompanying disease signature profiles, to describe chronic progressive degenerative diseases where (part) of the underlying biological system is known. The dynamics of the disease status in conjunction with the influence of symptomatic and protective treatment effects are characterized by a mathematical interpretation of biomarker information as a function of time.

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