Annex (glossary) : Advances in computational modeling approaches of pituitary gonadotropin signaling

I. Ordinary Differential equations

1) *Ordinary Differential Equation.* Mathematical equation that links the time derivative of a function y at time t with its current value at that time. In general, such an equation has the form

$$\frac{dy(t)}{dt} = f(t, y(t))\,, \forall t \geq 0\,, \quad y(t=0) = y_0\,. \qquad \text{(Equation 1)}$$

Given initial condition y_0 at time $t = 0$, and function f, appropriate analytical and/or numerical tools allow one to solve equation 1 to obtain the unknown function $t \mapsto y(t)$. This formalism is extensively used in mathematical physiology [1].

2) *(Non) Autonomous dynamical systems.* Equation 1 is said to be autonomous when the function f does not explicitly depend on time t. Non-autonomous dynamical systems are widely used in mathematical physiology to represent the impact of external rhythms (or inputs) not specifically included in the model. The same dichotomy autonomous / non-autonomous applies to all dynamical systems considered in this note.

3) *(Piecewise) Linear ODE.* Equation 1 is said to be linear if function f is a linear function in y. Classical one-dimensional examples yield to the Malthusian exponential growth model or the radioactive exponential decay (first order or one-step processes). The ODE is piecewise linear if the function f is piecewise linear (its graph consist of line segments).

4) *(Un)Damped harmonic oscillator.* The harmonic oscillator is a two-dimensional linear ODE, giving rise to oscillatory solution (like the pendulum or mass connected to springs). The harmonic oscillator is said to be damped if the amplitude of the oscillations

vanishes as time increases (decay to equilibrium position) or undamped otherwise (periodic solution).

5) *Goodwin model.* The Goodwin model describes negative feedback oscillators in cellular systems (such as lactose production in bacteria); its simplest form is given by a three-dimensional ODE

$$\begin{cases} \dfrac{dy_1}{dt} &= \gamma_1 \left(g(y_3) - y_1 \right) \, , \\ \dfrac{dy_2}{dt} &= \gamma_2 \left(y_1 - y_2 \right) \, , \\ \dfrac{dy_3}{dt} &= \gamma_3 \left(y_2 - y_3 \right) \, , \end{cases} \qquad \text{(Equation 2)}$$

where function g represents the feedback mechanism.

6) *Excitable systems.* Excitability refers to a phenomenon where a system has a single stable attractor, and two ways to return to equilibrium after perturbations. For small perturbations away from equilibrium, the return is monotonic; however, for perturbations beyond a threshold, the return is not monotonic, and undergoes a large excursion before settling down.

7) *The FitzHugh-Nagumo model.* The FitzHugh-Nagumo equation is a two-dimensional ODE that describes the essential features of the firing of a nerve. It is able to reproduce qualitative features of neural spikes, which are a typical example of excitability. It can also exhibit periodic solutions.

8) *Stiff nonlinear ODE with several timescales.* A system of linear ODEs is said stiff if the ratio between the largest and the smallest eigenvalue is large. By extension, for nonlinear systems, an ODE is said stiff if it involves several times scales of various different orders of magnitude, and requires dedicated numerical solvers to deal with.

9) *Biochemical reaction network.* A biochemical reaction network is defined by

• *Species. A finite set* $\mathcal{S} = \{S_1 \, , \cdots \, , S_d\}$ *of* $d \geq 1$ *species.*

• *Reactions. A finite set* $\mathcal{R} = \{R^1, \cdots, R^n\}$ *of* $n \geq 1$ relations between linear combinations of species, that is

$$R_i : \sum_{j=1}^{d} \alpha_j^i S_j \to \sum_{j=1}^{d} \beta_j^i S_j \, ,$$

where α_j^i, β_j^i are non-negative integers and called respectively reactant and product stoichiometric coefficients for reaction i and species j. The set of reactions defines a directed graph between linear combinations of species.

10) *Law of mass action.* A deterministic mass-action model associated with the biochemical reaction network $(\mathcal{S}, \mathcal{R})$ is given by the set of ordinary differential equations

$$\frac{dy_j}{dt} = \sum_{i=1}^{n} \left(\beta_j^i - \alpha_j^i\right) k_i \prod_{l=1}^{d} y_l^{\alpha_l^i} \, , \quad j = 1, 2, \cdots, d. \qquad \text{(Equation 3)}$$

The law of mass-action assumes that the rate of reaction R^i is proportional to the concentration of its reactants to the power of their stoichiometry. Constant k_i is called the rate constant of reaction R^i.

II. Ordinary Differential equations with event or jumps

1) *Reset decision functions.* A function that resets the value of the solution of an ODE when a specific condition is met (for instance when the solution exceeds a given threshold).
2) *Stepwise functions.* Functions that are defined piecewisely. The right-hand side of the ODE can change according to some specific conditions (for instance when the solution exceeds a given threshold).
3) *Threshold mediated transition.* Formalism that includes generic jumps for the value of the solution of an ODE when a specific condition is met (for instance when the solution exceeds a given threshold).

4) *Impulse ordinary differential equations.* Class of differential equations combining ODE with discrete jumps of the solution when specific conditions are met.

5) *Deterministic jump discontinuities.* Modification of the current value of the solution ruled by a non-continuous jump, which is pre-defined deterministically (no randomness in the instant of jump nor the magnitude of the jump).

6) *Dirac Delta functions.* Mathematical formalism representing impulses. A Dirac delta function can be seen as a function that equals zero everywhere except in one point where it is equal to infinity.

III. Algebraic-integro-differential equations

1) *Convolution integral.* Function given by an integral combining two functions in a very specific way. The convolution integral of two functions f and g is given by

$$I(t) = \int_0^t f(x)g(t-x)dx\,. \qquad \text{(Equation 4)}$$

In a pharmacokinetic context, if f is the rate of production of a chemical substance, and g the survival probability of that substance up to a time t, then $I(t)$ gives its current level at time t.

2) *Algebraic-integro-differential equation.* Equation involving algebraic relations, derivatives and integrals of functions. Algebraic relations give constraints to the values of one or several functions; differential terms involve the net rate of change of the functions; integrals typically involve the cumulative effect of the history of the values of a function.

IV. Delay differential equations

Mathematical equations linking the time derivative of a function y at time t with its current value at that time, together with the values at anterior times. For DDE involving a single fixed time delay, the equation has the form

$$\frac{dy(t)}{dt} = f\left(t, y(t), y(t-t_d)\right) \,, \forall t \geq 0 \,, \quad y(s) = y_0(s) \,, s \in [-t_d, 0) \,. \qquad \text{(Equation 5)}$$

Given initial condition y_0 on times $[-t_d, 0)$, and function f, appropriate analytical and/or numerical tools allow one to solve equation 5 to obtain the unknown function $t \mapsto y(t)$. This formalism is extensively used in mathematical physiology [1]. The delay may for instance represent the time needed to synthesize a molecule (which is not modeled in great details) .

V. Partial differential equations

Mathematical equations that link the partial derivatives of a function y of several variables (typically time and space, or other structuring variables like age, maturity) with its current value at that time.

1) *(Nonlinear) diffusion equations.* The linear diffusion equation, also called the heat equation, describes the constant isotropic diffusion of particles (or variation of temperature), and is written in its simplest one-dimensional form as

$$\frac{\partial u(t,x)}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial u(t,x)}{\partial x}\right) \qquad \text{(Equation 6)}$$

When D is non constant and depends on the solution itself ($D = D(x,u)$), the latter equation is called a nonlinear diffusion equation, and can represent crowding and/or anisotropic effects.

2) *Reaction diffusion equation.* A class of PDE combining diffusion equation 6 and biochemical reaction model 3.

3) *Structured cell populations.* Class of models involving PDE to describe the time evolution of cell populations together with some of their characteristics (like age, volume etc.).

VI. Stochastic differential equations

Mathematical equation that links the derivatives of a function y at time t with its current value at that time, perturbed by random dynamical systems (like Brownian motion for instance). The unknown function then becomes a random function with a given probability distribution, and is generally called a stochastic process.

1) *Stochastic point process, intensity.* A class of stochastic processes that is a collection of points randomly located on some underlying mathematical space. Point processes can be used as mathematical models of phenomena representable as points in some type of space (like discrete events in time). Roughly, for a point process, the intensity refers to the function ruling the (mean) rate of apparition of new points. In molecular biology, the transcription process (synthesis of new mRNA upon stimulation) is typically modeled using such formalism.
2) *(Weibull) renewal process.* A renewal process is a point process for which the time between any two successive events only depends on the value of the process at the lastest event that has occurred. A Weibull renewal process is a particular kind of renewal process for which the interevent times follow a Weibull distribution.
3) *Generalized gamma density.* A specific probability distribution with three parameters (generalizing the exponential, the Weibull and the Gamma distribution), generally used to represent the complete duration of a sequence of coordinated random events (like the cell cycle for instance).
4) *Ornstein-Uhlenbeck process.* Stochastic process describing the velocity of a massive Brownian particle under the influence of friction.

VII. Stability and Bifurcation for dynamical systems

Stability and bifurcation theory for dynamical systems aims to characterize the long time behavior of a dynamical system, and in particular to know if the system reaches an equilibrium or not as time goes to infinity.

1) *Locally asymptotically stable.* An equilibrium for a dynamical system is locally asymptotically stable if any trajectory starting from a small perturbation away from that equilibrium converges to the same equilibrium as time goes to infinity.
2) *(Hopf) bifurcation.* Critical point where a system's stability switches: in a (supercritical) Hopf bifurcation, a stable equilibrium point becomes unstable and a periodic solution arises.

VIII. Statistical tools

1) *Deconvolution methods.* Statistical algorithms aiming to recovering a signal that has been convoluted by some other signal. For instance, recording the signal I from equation 4 , one wishes to recover f (knowing some properties of g).
2) *Regularization scheme.* Regularization is a process of introducing additional information in order to solve an ill-posed problem or to prevent overfitting. In deconvolution methods, this consists typically in imposing some restriction to the unkown signal in order to be able to better identify its parameters.

IX. Pharmacology

1) *Physiologically-based pharmacokinetic model.* Mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion of synthetic or natural chemical substances in humans and other animal species. These models typically consists of system of (ordinary) differential equations.
2) *Equilibrium pharmacology model.* Class of models aiming to describe dose-response relationship (without kinetics). These models can often be derived as equilibrium of deterministic mass-action models like equation 3.
3) *Operational model.* A classical example of pharmacology models describing agonist-induced dose-response relationships. The model was first introduced by [2].

REFERENCES

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