Discrete Approximations of Continuous Models

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The general problem

Suppose we have a natural system $N$ and some variables $\vec{v}(t)$ that change over time. We can consider mathematical models $M_0$, $M_1$ that predict the dynamics of the variables $\vec{v}$.

When can we be assured that models $M_0$, $M_1$ make equivalent predictions about the variables $\vec{v}$?

With some appropriate definitions, this question can be turned into a mathematical problem; whereas the question whether the model makes true predictions about $\vec{v}$ is empirical and goes beyond mathematics.
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The models $M_0, M_1$ may be of different types: ODE, PDE systems, discrete-time systems with a continuous or discrete state space (e.g. Boolean), or even stochastic processes of various kinds.

The meaning of equivalent predictions is far from obvious when $M_0, M_1$ are of different types. In general, the precise definition will depend on the particular aspects of the dynamics that $M_0, M_1$ are supposed to model.
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Let $M_1$ denote the resulting model.
It is difficult to measure actual mRNA concentrations with reasonable accuracy. But it is easy to take fuzzy snapshots of mRNA levels at different times even for all genes of an organism simultaneously using microarrays. These snapshots reveal only whether the expression level of a gene is high or low (sort of). One is thus tempted to construct a model $M_0$ of gene regulation that is a Boolean system, where
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All these assumptions are biologically unrealistic.
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  $\vec{s}(\tau + 1) = f(\vec{s}(\tau))$.

The $i$-th component $f^i : \{0, 1\}^n \to \{0, 1\}^n$ of $f$ is called the regulatory function of gene number $i$. Note that $M_0$ is uniquely determined by $f$. 
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What is the role of separation of timescales and intermediaries in this phenomenon?
Under what conditions is $M_0$ guaranteed to be a good approximation of $M_1$?
In other words, which conditions guarantee that a DE model $M_1$ will exhibit switchlike behavior?
What is an approximation in this context? Comparing apples with oranges

The mRNA concentrations $\vec{v}$ of $N$ will be represented by vectors $\vec{x}$ of reals in $M_1$ and Boolean vectors $\vec{s}$ in $M_0$. We can fix a discretization $S$ that maps real vectors $\vec{x}$ to Boolean vectors $\vec{s} = S(\vec{x})$. Then we can consider $M_0$ a good approximation of $M_1$ if for each ODE trajectory $\vec{x}(t)$ that starts from initial condition $\vec{x}(0) \in U$ for some large enough $U$ the corresponding discretized trajectory $S(\vec{x}(t))$ is consistent with the Boolean trajectory $\vec{s}(\tau)$, where $\vec{s}(0) = S(\vec{x}(0))$, that is, if the updating function $f$ of $M_1$ correctly predicts, at all future times, which discretized state will be entered next by the DE trajectory. All of numerical analysis is essentially based on this type of construction, except that there the concern is with not exceeding the error tolerance over a finite time interval.
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- If $\vec{s}(\tau + 1) = f(\vec{s}(\tau))$ in all such situations, we have strong consistency.

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Recordings from certain neuronal tissues (of real organisms) reveal the following pattern: Time seems to be partitioned into episodes with surprisingly sharp boundaries. During one episode, a group of neurons fires, while other neurons are at rest. In the next episode, a different group of neurons fires. Group membership may vary from episode to episode, a phenomenon called dynamic clustering.
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Why? Can we mathematically explain this phenomenon?
Each excitatory (E-) cell satisfies
\[
\frac{dv_i}{dt} = f(v_i, w_i) - g_{EI} \sum s_j(v_i - v_{syn}^j)
\]
\[
\frac{dw_i}{dt} = \epsilon g(v_i, w_i)
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\[
\frac{ds_i}{dt} = \alpha(1 - s_i)H(v_i - \theta_E) - \beta s_i.
\]

Each inhibitory (I-) cell satisfies
\[
\frac{dv_i^I}{dt} = f(v_i^I, w_i^I) - g_{IE} \sum s_j(v_i^I - v_{syn}^I) - g_{II} \sum s_j(v_i - v_{syn}^I)
\]
\[
\frac{dw_i^I}{dt} = \epsilon g(v_i^I, w_i^I)
\]
\[
\frac{dx_i^I}{dt} = \epsilon \alpha_x(1 - x_i^I)H(v_i^I - \theta_I) - \epsilon \beta_x x_i^I
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\[
\frac{ds_i^I}{dt} = \alpha_I'(1 - s_i^I)H(x_i^I - \theta) - \beta s_i^I.
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Can we analyze the dynamics of this model?

The architecture involves a layer of excitatory neurons and a layer of inhibitory neurons that mediate the firing of the excitatory neurons. The whole layer acts as a pacemaker.
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Let us call the model that we just described $M_1$. 
The following is true in at least some neuronal networks.

- Neurons fire or are at rest.
- After a neuron has fired, it has to go through a certain refractory period when it cannot fire.
- A neuron will fire when it has reached the end of its refractory period and when it receives firing input from a specified minimal number of other neurons.

Let us build a simple model $M_0$ of neuronal networks based on these facts.
A Discrete Dynamical System Model

A directed graph $D = (V_D, A_D)$ and integers $n$ (size of the network), $p_i$ (refractory period), $th_i$ (firing threshold).
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A state $\vec{s}(\tau)$ at the discrete time $\tau$ is a vector: $\vec{s}(\tau) = (s_1(\tau), \ldots, s_n(\tau))$ where $s_i(\tau) \in \{0, 1, \ldots, p_i\}$ for each $i$. The state $s_i(\tau) = 0$ means neuron $i$ fires at time $\tau$. 
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Dynamics on the discrete network:
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Dynamics on the discrete network:

- If $s_i(\tau) < p_i$, then $s_i(\tau + 1) = s_i(\tau) + 1$.
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If $p_i = 1$ for all $i$ then this is a Boolean system.
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Theorem

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Theorem

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We would really like to know what kind of architectures in general favor or imply consistency of a ODE system with a Boolean system. In particular, we want to understand the role of separation of timescales and of intermediary variables.
Recall the following notions

Let \( t \) denote time in the ODE model \( M_1 \), let \( \tau \) denote time in the Boolean approximation \( M_0 \). Consider a time \( t_{\text{switch}} \) when

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- Other notions of consistency are meaningful if we can treat changes in the Boolean state of several variables that occur in very short intervals as simultaneous.
Leon Glass and his followers have produced a large body of work on consistency (but not in general strong consistency) between so-called piecewise linear ODE models of gene regulatory networks and their Boolean approximations. Again, the right-hand sides of the ODEs in these models have discontinuities.

Our plan

Construct classes $\mathcal{D}$ of toy ODE models such that

- The ODEs for individual variables are easy to understand.
- The right-hand sides of the ODEs are Lipschitz-continuous.
- The class $\mathcal{D}$ is universal in the sense that each Boolean system $M_0$ can be treated as a (not necessarily consistent) natural approximation of a system $M_1 \in \mathcal{D}$.
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In order to achieve \textit{universality} of our class \( \mathcal{D} \) we need to translate a Boolean system with updating function \( f \) into ODE systems \( D(f, \vec{\gamma}) \), where \( \vec{\gamma} \) is a vector of parameters.
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The paper discusses several natural classes of conversion schemes.
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The ODEs

Let \( g(x) = 3x - x^3 - 3 \).
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The ODE for variable \( i \) will take the form
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\dot{x}_i = \gamma_i (g(x_i) + 6Q_i(x)),
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where \( Q_i \) is the \( i^{th} \) coordinate of a given conversion \( Q = Q^f \), and \( \gamma_i \) is a positive constant that allows us to implement separation of time scales.
\[
\dot{x}_i = \gamma_i (g(x_i) + 6Q_i(x_i)), \text{ where } g(x) = 3x - x^3 - 3. \text{ Think of } Q_i \text{ as a constant.}
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\[ \dot{x}_i = \gamma_i(g(x_i) + 6Q_i(\vec{x})), \text{ where } g(x) = 3x - x^3 - 3. \text{ Think of } Q_i \text{ as a constant.} \]

- If \( Q_i < 1/6 \), there exists a unique globally stable equilibrium \( x_i^* < -1 \).

\[ [\ -2\ 1038, \ 2\ 1038] \]

\( 2n \) is forward invariant and can be considered the state space of our ODE systems.
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\[ \begin{array}{ll}
2.1038 & 2.1038 \\
\end{array} \]

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- If \( Q_i > 5/6 \), there exists a unique globally stable equilibrium \( x_i^{**} > 1 \).
- If \( Q_i \in (1/6, 5/6) \), there exist three equilibria, locally stable ones \( x_i^* < -1 \) and \( x_i^{**} > 1 \), as well as an unstable one \( -1 < x^o < 1 \).
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- \([-2.1038, 2.1038]^{2n}\) is forward invariant and can be considered the state space of our ODE systems.
An example

Let $Q_i$ be a nondecreasing function that takes the value 0 whenever $x_j \in (-\infty, -1]$ and takes the value 1 whenever $x_j \in [1, \infty)$. We can think of $Q_i$ as the $i^{th}$ coordinate of a conversion of a Boolean function $f$ with $f_i(\vec{s}) = s_j$.

Consider $\dot{x}_i = \gamma_i (g(x_i) + 6Q_i(\vec{x}))$, where $g(x) = 3x - x^3 - 3$ and an initial state where $x_i(0) \in (-\infty, -1]$ while $x_j(t) \in [1, \infty)$ for all times $t$. Then $Q_i > 5/6$, so there exists a unique globally stable equilibrium $x^*$. Variable $i$ will move into the interval $[1, \infty)$ and thus will eventually change its Boolean state to 1, as predicted by the Boolean updating function.

This example allows us to incorporate equations into our system that essentially copy the Boolean value of some variable $j$ to variable $i$, at whatever time scale we choose.
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This example allows us to incorporate equations into our system that essentially copy the Boolean value of some variable $j$ to variable $i$, at whatever time scale we choose.
Think of \( n \) variables of a natural system \( N \) whose dynamics we are interested in. We will represent them in our ODE systems as variables \( x_1, \ldots, x_n \), called signature variables. We are interested in achieving (strong) consistency with the dynamics of their Boolean counterparts \( s_1, \ldots, s_n \) as governed by a Boolean updating function \( f \).
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To achieve this goal, we will need additional signaling variables $x_{n+1}, \ldots, x_{2n}$ that will not have counterparts in the Boolean approximation.
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We construct a system $D(f, \vec{\gamma})$ by choosing the DE for each signature variable $x_i$ as in the example on the previous slide, with $j = x_{n+i}$ (so the value of the signaling variable gets essentially copied to the corresponding signature variable).
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The signaling variable $x_{n+i}$ takes input from the signature variables only, with $Q_{n+i}$ being a conversion of the Boolean regulatory function $f_i$. 
Consider the one-dimensional Boolean system $M_0$ given by the updating function
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But we get strong consistency with \( D(f, \vec{\gamma}) \) for any \( \vec{\gamma} \).
Strong consistency is possible only for some Boolean systems

Consider a Boolean system $M_0$ with updating function $f$. We say that $f$ (or $M_0$) is one-stepping if for every $\vec{s}$ the Boolean vectors $\vec{s}$ and $f(\vec{s})$ differ in at most one coordinate.
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**Lemma**

A Boolean system can be strongly consistent with an ODE system $M_1$ for any reasonable discretization only if $M_0$ is one-stepping.
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**Lemma**

A Boolean system can be strongly consistent with an ODE system $M_1$ for any reasonable discretization only if $M_0$ is one-stepping.

**Proof:** For any discretization with nice enough boundaries, most trajectories of $M_1$ will cross only one boundary at a time.
Theorem

Let $M_0$ be a Boolean system with a **one-stepping** updating function $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ and let $\vec{\gamma}^- = (\gamma_1, \ldots, \gamma_n)$ be a fixed vector of positive reals. Then there exist $\mu > 0$ such that for every extension of $\vec{\gamma}^-$ to a $2^n$-dimensional vector $\vec{\gamma}$ of positive reals with $\gamma_i + n < \mu$ for all $i$, the systems $M_0$ and $D(f, \vec{\gamma})$ are strongly consistent.

We have already seen that the assumption that $f$ is one-stepping is necessary in this theorem.
A Theorem

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A Theorem

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A more general Theorem

We also have a more technical notion of **monotone-stepping** Boolean functions. All one-stepping Boolean functions are monotone-stepping, but not *vice versa*.

**Theorem**

*Let $M_0$ be a Boolean system with a **monotone-stepping** updating function $f : \{0, 1\}^n \to \{0, 1\}^n$ and let $\vec{\gamma}^- = (\gamma_1, \ldots, \gamma_n)$ be a fixed vector of positive reals. Then there exist $\mu > 0$ such that for every extension of $\vec{\gamma}^-$ to a $2n$-dimensional vector $\vec{\gamma}$ of positive reals with $\gamma_{i+n} < \mu$ for all $i$, the systems $M_0$ and $D(f, \vec{\gamma})$ are consistent.*
Some additional assumption on \( f \) is needed in the last theorem, but the assumption that \( f \) is monotone-stepping is too strong. It remains open to find a necessary and sufficient condition on \( f \) for which the conclusion of the last theorem holds.
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The particular form of the DEs in our class $\mathbb{D}$ allowed us to find the proofs of the above theorems, but the argument really seems to require only a particular type of interacting bifurcations. It remains to formulate and prove versions of the theorems in such a more general form.
How about arbitrary functions? The second theorem can be extended to some, but not all Boolean functions. But we know (not yet published) that of $M_0$ is an arbitrary Boolean system, then $M_0$ is consistent with some ODE system $M_1$. This follows from the observation that every Boolean system can be embedded into a one-stepping Boolean system with additional Boolean variables, which allows to construct $M_1 \in D$, but with a more complicated relationship between $M_0$ and $M_1$. In effect, $M_1$ will have a lot more intermediary variables. The particular forms of the DEs for the intermediary variables may not matter all that much. We can think of $M_1$ as a network of intermediary (signaling) and signature variables. What structural properties of this network favor or imply consistency?
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