Boolean vs. ODE models of gene regulatory and other systems

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Many biological systems exhibit switch-like behavior. Examples include gene-regulatory networks where at a given time a gene may be either expressed or not expressed, neuronal networks, where a neuron may either be firing or resting, in SI or SIS disease dynamics, an individual can be either infectious or susceptible.
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Such systems often can be modeled either by ODE systems or by Boolean networks that distinguish only on and off states.
Modeling with ODE vs. Boolean systems

ODE models are based on biologically more realistic assumptions and are expected to make more reliable predictions. However, it is usually impossible to study them analytically, and for large systems even numerical explorations of such models may be infeasible.

Boolean models are much easier to study, but they are further removed from biological reality.

When can we be assured that a Boolean model $B$ and an ODE model $D$ of the same biological system make qualitatively equivalent predictions?
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What do you mean by *the same*?

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The first step is to discretize relevant variables.
Examples of discretization

- In gene regulation, one may distinguish mRNA concentrations below a threshold $\Theta$ from mRNA concentrations above a threshold $\Theta$.
- In modeling neuronal networks, one may distinguish cross-membrane voltages below a threshold $\Theta$ from cross-membrane voltages above a threshold $\Theta$.

Note that in both of these examples only some variables of the system are being assigned Boolean values 0 or 1. Other variables of the ODE system (gene product concentrations, gating variables) are being ignored in these examples.
Another example of discretization

In modeling infectious diseases, an individual is classified as infectious if the viral load is above a threshold $\Theta_v$.

This discretization now can be used to build either agent-based stochastic Boolean models $\mathbb{B}_{agent}$ or deterministic ODE $SI$ or $SIS$ models $\mathbb{D}$. The latter are based on the proportion of individuals in the $I$-class.
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Now one could study a second discretization based on whether this proportion is below or above a threshold $\Theta_c$ and compare the predictions of the resulting Boolean model $B_{system}$ with those of $D$. 
A formal definition of discretization of variables

First we need to choose partitions of the state space $S$ of the ODE system $D$ into disjoint regions ($R_i^0, R_i^1$). Then we can assign to every state $\vec{x}$ of the ODE system $D$ a corresponding Boolean state $\vec{s} = \Phi(\vec{x}) \in S_B$ such that $s_i = 0$ $\Leftrightarrow$ $\vec{x} \in R_i^0$, where $s_i$ denotes the $i$-th coordinates of $\vec{s}$.

Note that the dimensions of the resulting Boolean vectors do not need to be the same as those of $\vec{x}$.

Note also that an analogous procedure also works for discretizing the ODE states into more than two regions and discrete models with more than two states per variable.
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First we need to choose partitions of the state space $S_D$ of the ODE system $\mathbb{D}$ into disjoint regions $(R_0^i, R_1^i)$. Then we can assign to every state $\vec{x}$ of the ODE system $\mathbb{D}$ a corresponding Boolean state $\vec{s} = \Phi(\vec{x}) \in S_B$ such that

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The map $\Phi : S_D \to S_B$ gives us, for every initial state $\vec{x}(0) \in S_D$, a function $\Psi_{\vec{s}(0)} : [0, \infty) \to S_B$ such that $\Psi_{\vec{s}(0)}(t) = \Phi(\vec{s}(t))$ for all $t \in [0, \infty)$. Let us call this the **continuous-time Boolean trajectory** $\Delta(\vec{x}(0))$.  

Now we need to turn this into an actual **discrete-time Boolean trajectory**. The most natural idea would be define $\Delta(\vec{x}(0)) = (\vec{s}(0), \vec{s}(1), \vec{s}(2), \ldots)$ as the sequence of successive Boolean states that we observe in $\Psi_{\vec{s}(0)}(0)$. 

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as the sequence of **successive** Boolean states that we observe in $\Psi_{\vec{s}(0)}$. 
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Given $D, B$, an open region $U$ of $S_D$, and the updating function $f$ of $B$, we say that $B$ is **strongly consistent with** $D$ **on** $U$ if for all $\vec{x}(0) \in U$ and all $\tau \in \mathbb{N}$:

$$\vec{s}(\tau + 1) = f(\vec{s}(\tau)), \quad (1)$$

where $(\vec{s}(0), \vec{s}(1), \vec{s}(2), \ldots) = \Delta(\vec{x}(0))$. 

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If (1) holds for some $U$ as above such that $\Phi$ maps $U$ onto the state space of $\mathcal{B}$, then we say that $\mathcal{D}$ realizes $\mathcal{B}$.
Strong consistency may be too much to hope for

Think about a two-dimensional Boolean system $B$ where $f(s_1, s_2) = 11$ iff $s_1 = s_2 = 0$ and $f(s_1, s_2) = 00$ otherwise. Consider a discretization of $(x_1 x_2) \in S_D$ based on thresholds $\Theta_1, \Theta_2$. 
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Now if for all $\vec{x}(0)$ and all $\tau \in \mathbb{N}$

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\textbf{cannot} have strong consistency with $\mathbb{B}$ on the whole state space of
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But we need (2) only for all $\vec{x}(0) \in U$; so $\mathbb{B}$ may still be \textbf{realized}
by some ODE systems $\mathbb{D}$. 

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We want to prove that biologically relevant \textbf{classes} of ODE systems have consistent Boolean approximations. We can try:

- Focus on some interesting $U$.
- Focus on some interesting classes of Boolean systems.
- Weaken the notion of strong consistency.
- Tinker with the definition of the discrete-time Boolean trajectory.
- Study these problems for some toy models first.

In the remainder of this talk I will briefly review some research that has been done along these lines.
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An interesting class of Boolean systems

Let us call a Boolean system **one-stepping** if

\[ H(\vec{s}(\tau), \vec{s}(\tau + 1)) \leq 1 \]

for all \( \tau \) along each trajectory where \( H \) denotes Hamming distance. For one-stepping Boolean systems simultaneous crossing of thresholds in the ODE system is not an issue. These Boolean systems can be realized in the sense of strong consistency by many classes of ODE systems.

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- Just *et al.* for a class of toy models.
- Later talks in this session.
Dynamic clustering in neuronal networks

In several neuronal networks, it has been observed that time appears to progress in distinct episodes in which some subpopulation of cells fire synchronously; however, membership within this subpopulation may change over time. That is, two neurons may fire together during one episode but not during a subsequent episode. This phenomenon is called **dynamic clustering**.
How to explain dynamic clustering?

This is a strange phenomenon. As far as is known, there is no central pacemaker in these networks. The episodes are an emergent property of the internal dynamics of individual neurons and their interactions.
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Problem: Are there classes of ODE models, based on Hodgkin-Huxley equations for individual neurons that exhibit dynamic clustering? If so, can the firing patterns be predicted by Boolean approximations?
A theorem

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In this theorem we use a version of strong consistency that is based on a slightly altered definition of $\Delta(\vec{s}(0))$; essentially the episodes give us a neat way to discretize time and “next Boolean state” is determined by which neurons fire during the episode; we ignore the slight fuzziness at the boundaries of the episodes.
Instead of demanding

$$\vec{s}(\tau + 1) = f(\vec{s}(\tau)), \quad (3)$$

where \((\vec{s}(0), \vec{s}(1), \vec{s}(2), \ldots) = \Delta(\vec{x}(0))\) where \(\vec{s}(0) \in U\) we could just require that
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The classical work of Leon Glass and his collaborators shows that this form of consistency holds for Boolean approximations of a large class of piecewise linear ODE systems.
A class of toy models

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Some results for the toy model

One can get strong consistency under sufficient separation of time scales for all one-stepping Boolean systems. For some one-stepping Boolean systems this works only if each agent has at least two variables. Every Boolean system can be embedded in a one-stepping Boolean system. Thus with some coding and larger agents, one can get strong consistency for all Boolean systems.
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Directions for further research

- Larger agents (more intermediate variables that will be ignored in the Boolean model) seem to favor consistency.
- How generic is this phenomenon?
- Investigate weak consistency for our toy models.
- Investigate notions of $\varepsilon$-consistency where switches of the Boolean state that occur within $\varepsilon$ real time units are treated as simultaneous.
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The research group that worked on the toy models included Todd R. Young (Ohio University) and our students Ben Elbert, Mason Korb, Bismark Oduro, and Hanyuan Zhu.

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