Modeling electrical activities of gonadotropin-releasing hormone neurons

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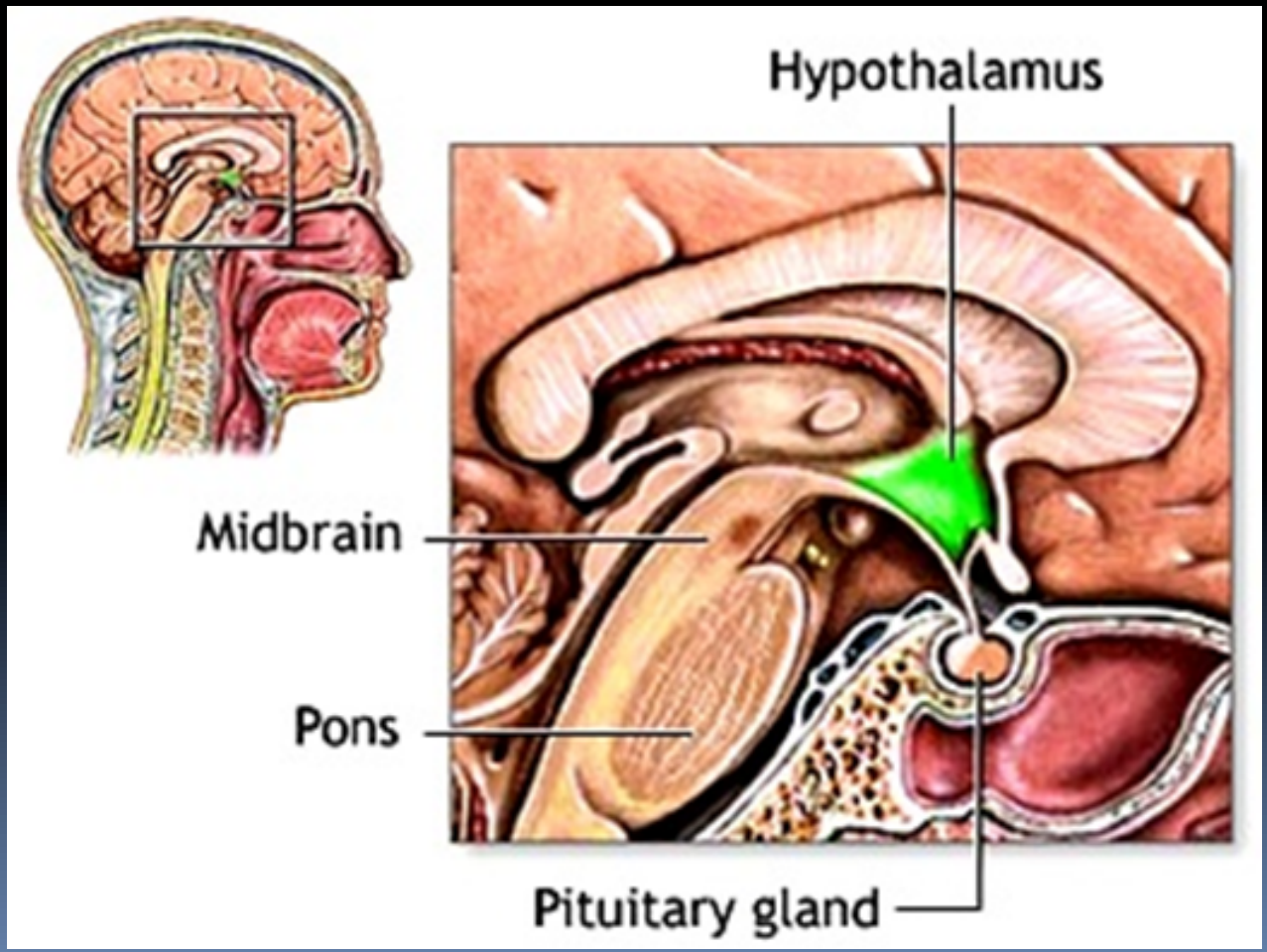
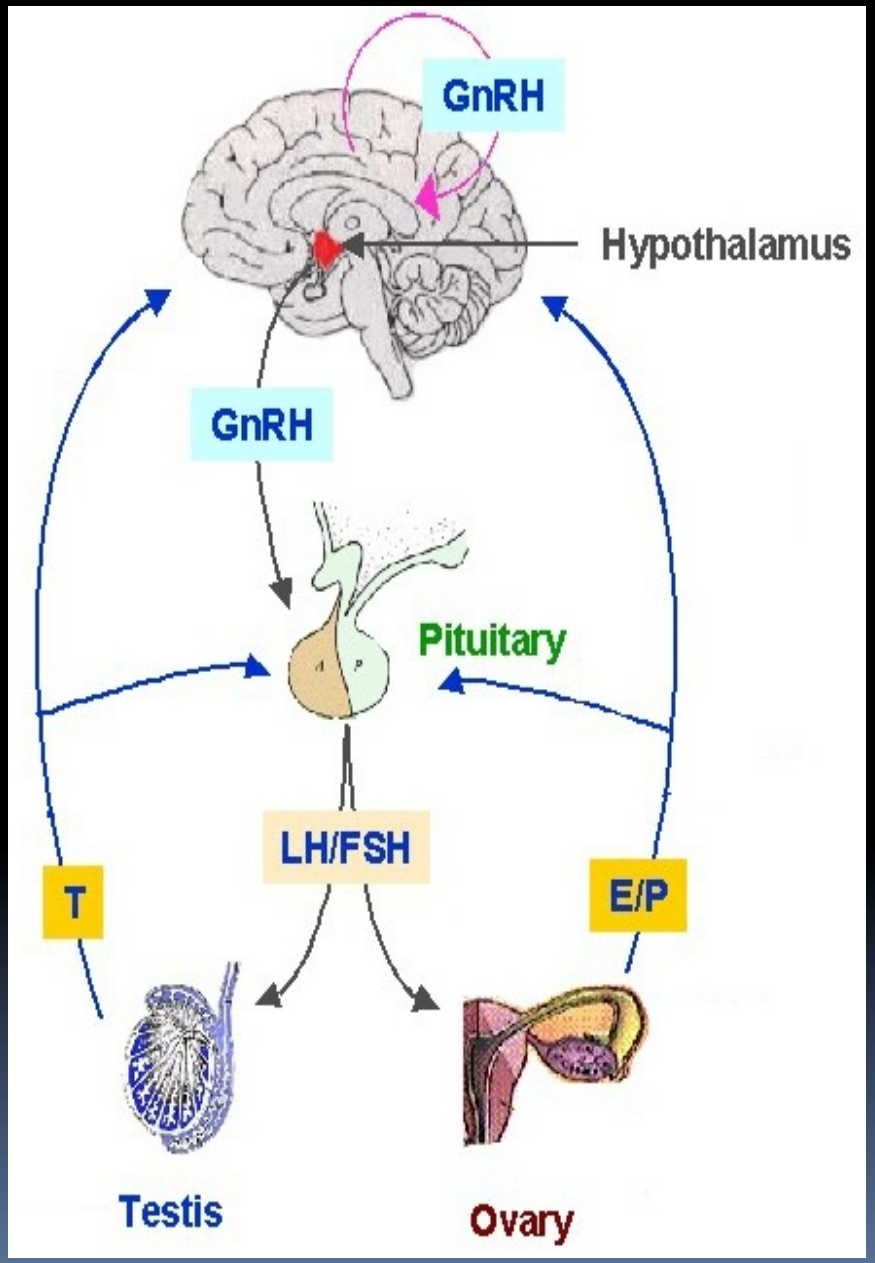
Overview of GnRH neurons

- A neuroendocrine network, located in the hypothalamus.
- It consists of about 4000 neurons.
- It exhibits hormonal and electrophysiological rhythms that occur at different time scales.

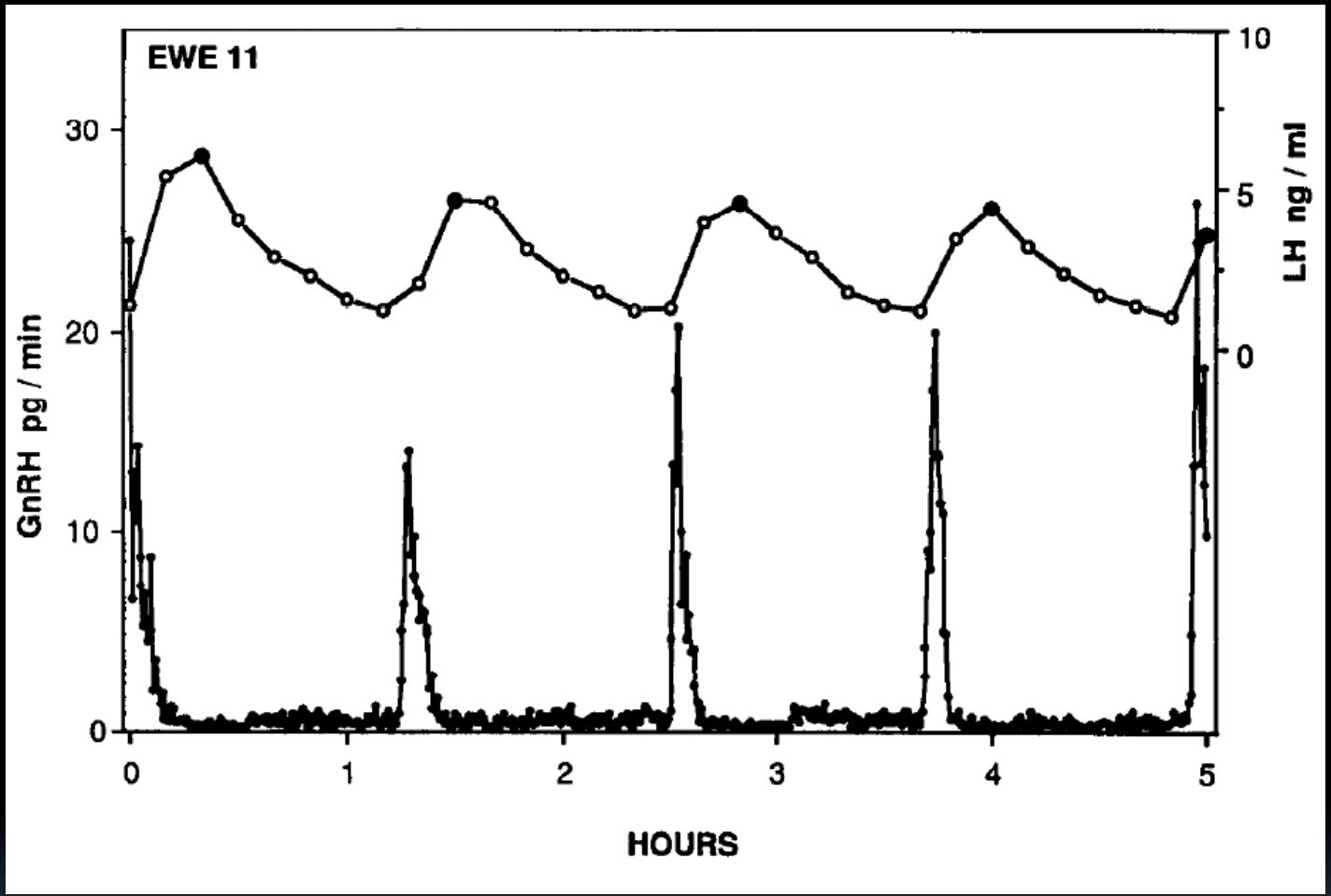


GnRH release

- GnRH hormone is released synchronously to control fertility. It stimulates LH/ FSH secretion.
- LH/FSH in turn stimulate secretion of steroidal hormones from the gonads.



GnRH release



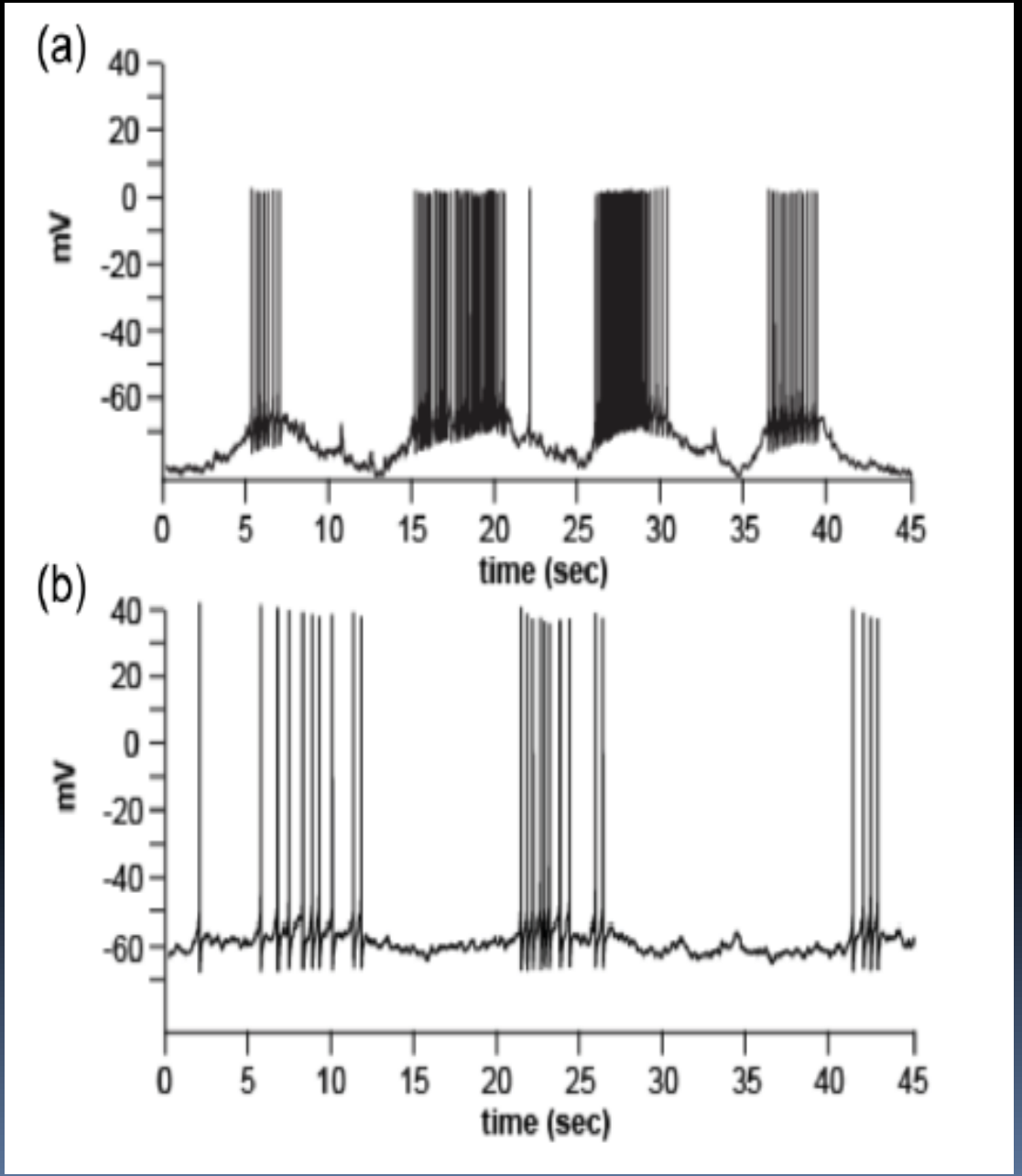
- Hormone secretion is pulsatile and episodic.
- Pattern of secretion is important for fertility.

GnRH electrical activities

1. GnRH neurons also exhibit bursting behavior.

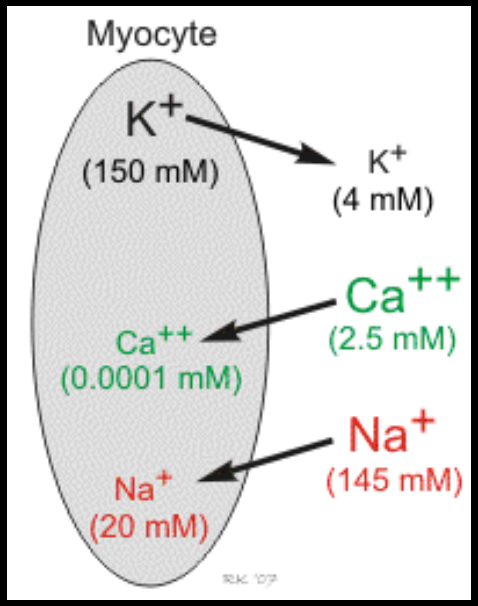
2. 1-2% of neurons are parabolic bursters. Most are irregular bursters.

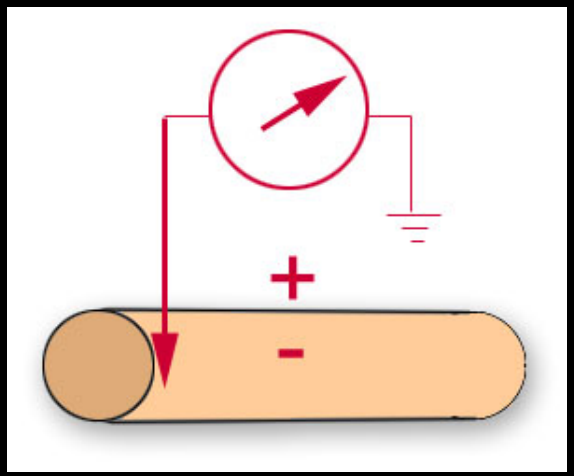
3. You can develop a HH-type model to explain how the two bursts are generated.



Membrane electrical activities

1. There are voltage and chemical gradients across cell membranes.





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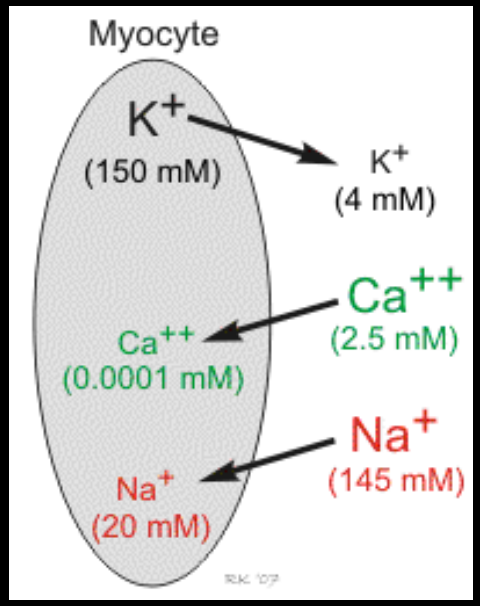
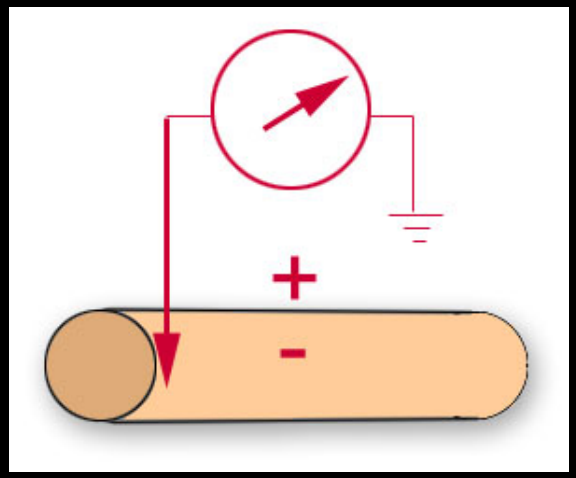
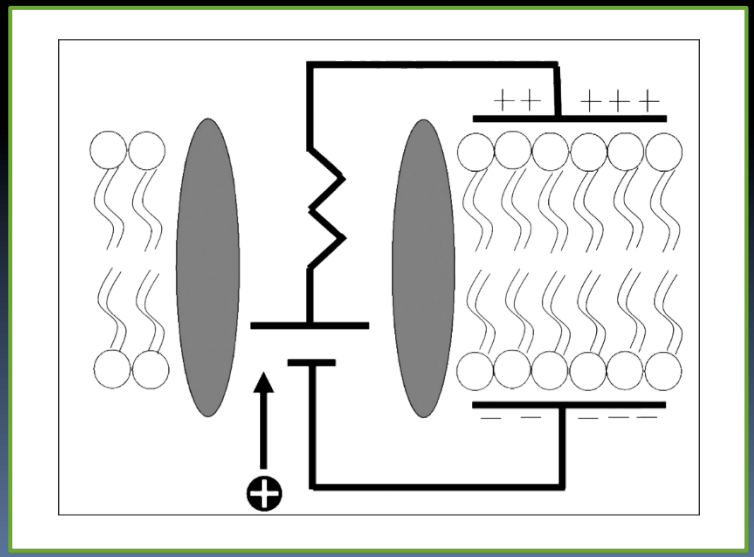


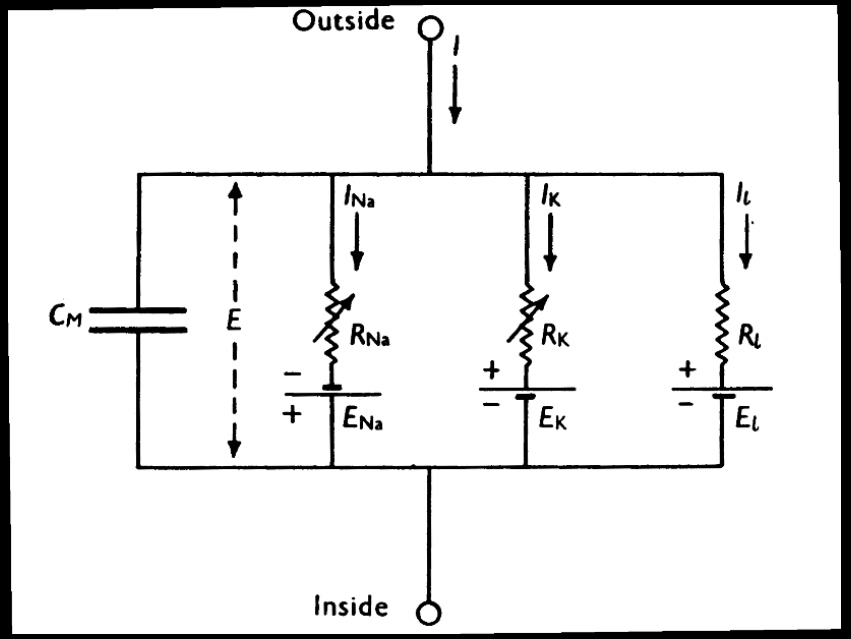


2. Cell membranes are lipid bilayers that express ion channels (e.g., Na^+, K^+, Ca^{2+}, channels). They can be thought of as electrical circuits.

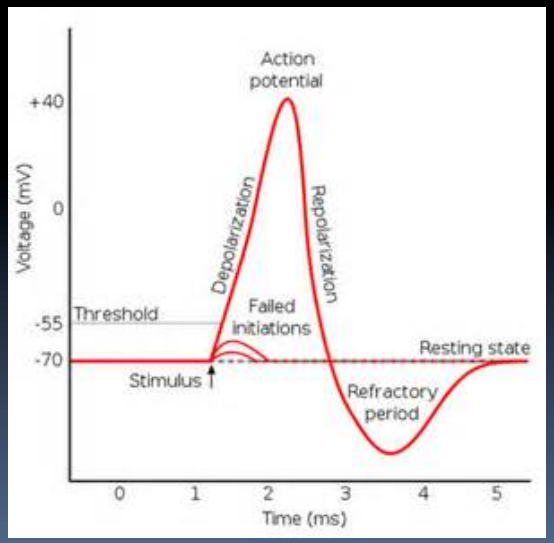


Membrane electrical activities

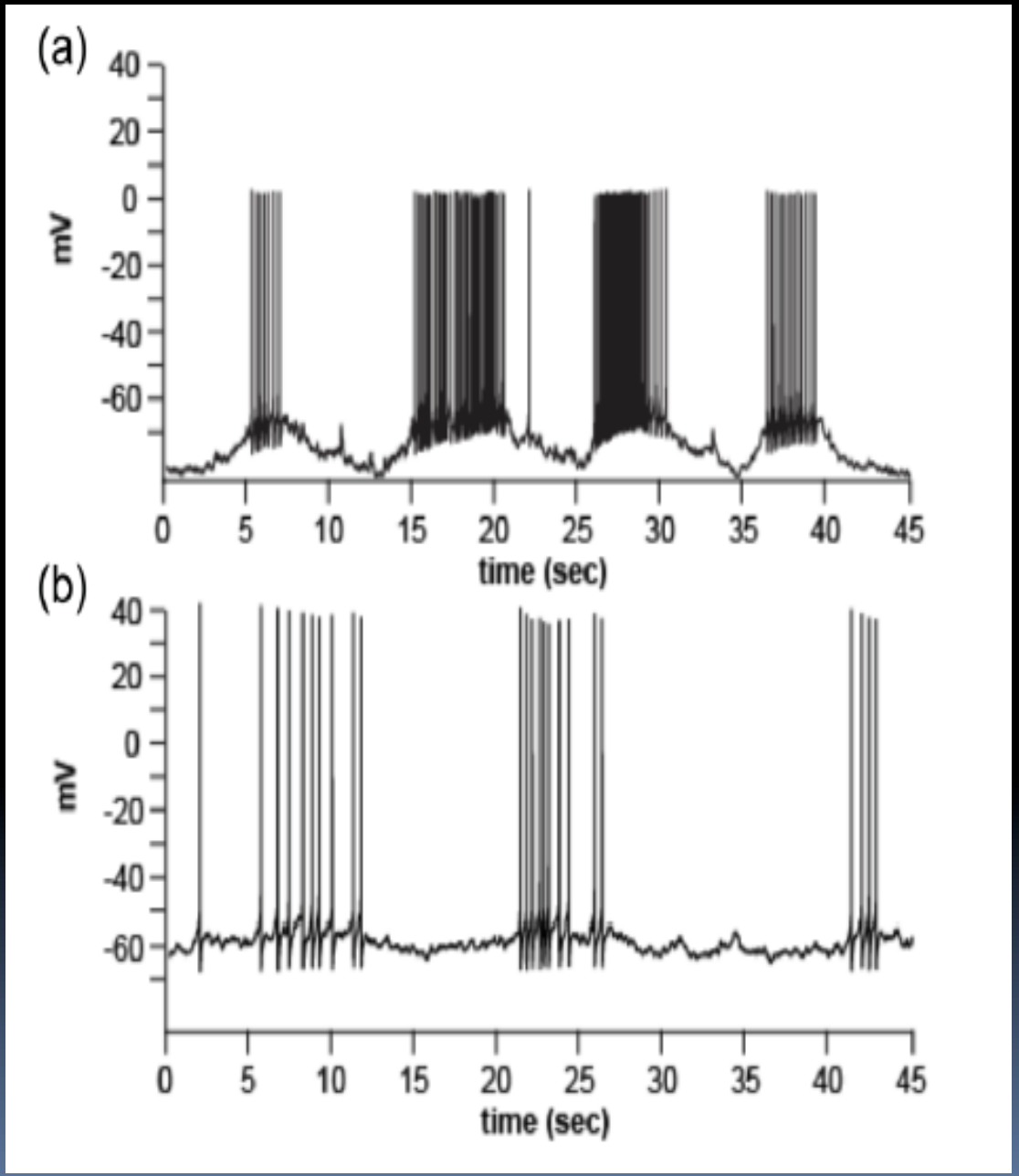
1. Hodgkin and Huxley developed in 1952 the HH model that describes the electrical activities of neurons.



2. The model can produce an action potential.



GnRH electrical activities



Mathematical model for GnRH

The HH-type model with Ornstein-Uhlenbeck noise is given by

$$C_m \frac{dV}{dt} = -(I_{NaF} + I_{NaP} + I_A + I_K + I_{HVA} + I_{LVA} + I_s + I_h + I_{KCa} + I_L) + I_{app} + \eta(t),$$

$$t_c d\eta(t) = -\eta(t)dt + \sqrt{2Dt_c}dW(t), \quad \eta(0) = \eta_0,$$

$$I = gm^p h(V - E),$$

$$h = \sum_{i=1}^{n} f_i h_i, \quad 0 \le f_i \le 1, \quad \sum_{i=1}^{n} f_i = 1$$

$$\dot{m} = \frac{m_\infty(V) - m}{\tau_m(V)}$$

$$\dot{h_i} = \frac{h_\infty(V) - h_i}{\tau_{h_i}(V)}$$

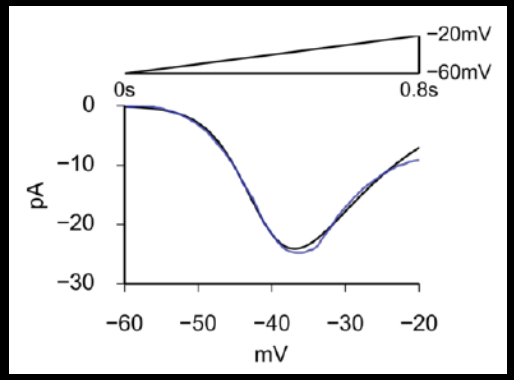
$$x_\infty(V) = \frac{1}{1 + \exp[(V - V_h)/k]}, \quad x = m, h.$$

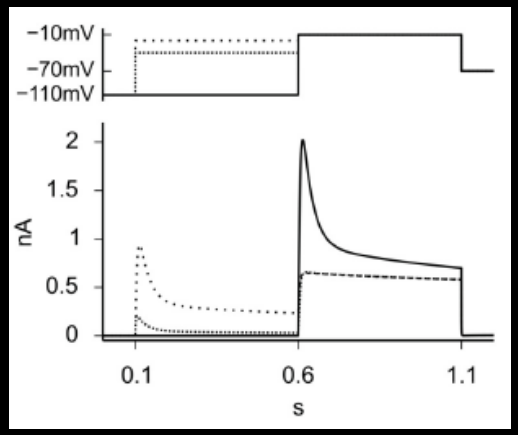
$$\frac{dCa}{dt} = f(-\alpha I_{Ca} - k_p \frac{Ca^2}{K_p^2 + Ca^2})$$

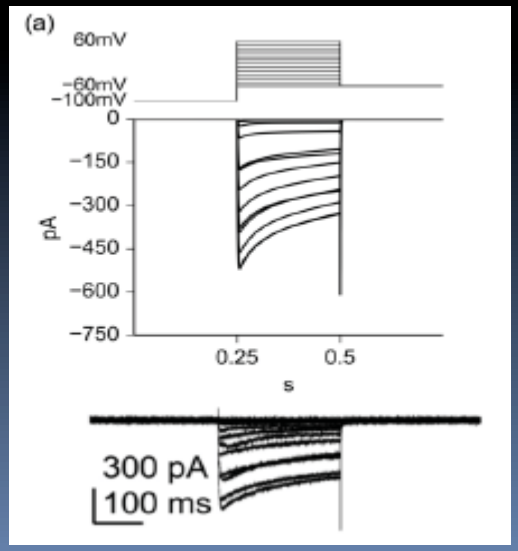
$$I_{Ca} = I_{LVA} + I_{HVA} + I_s$$

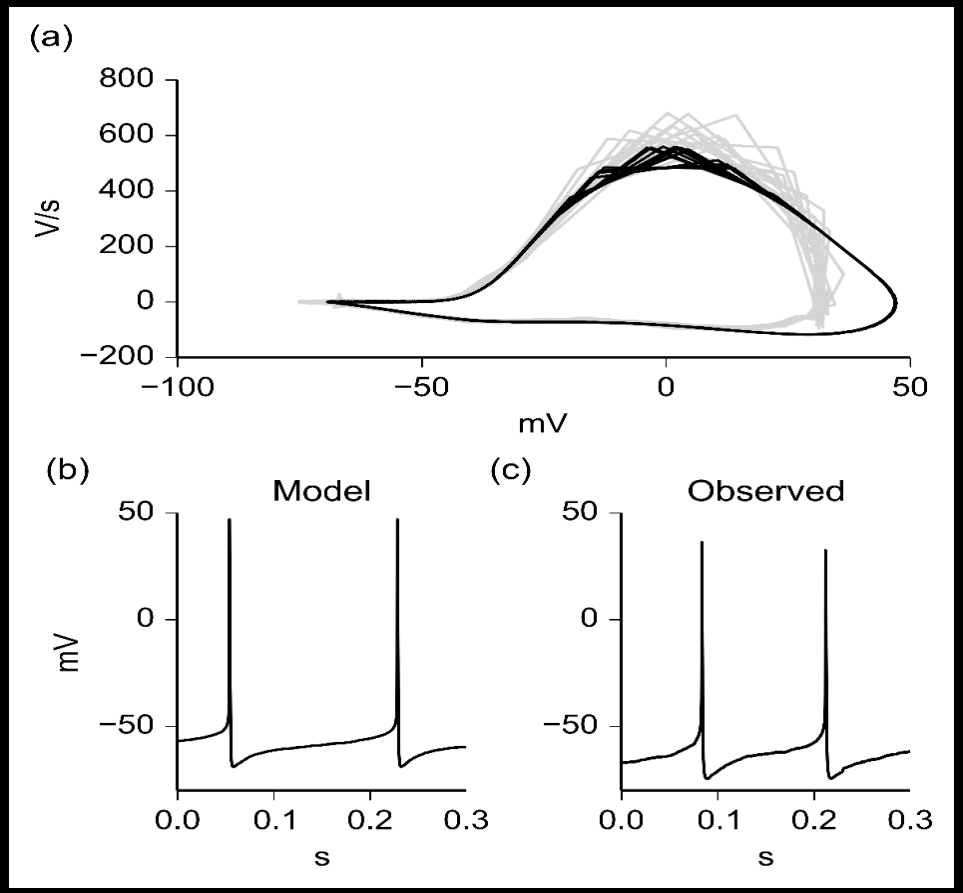
$$\alpha = \frac{\beta}{2FV_{cyt}},$$

Current and burst fittings







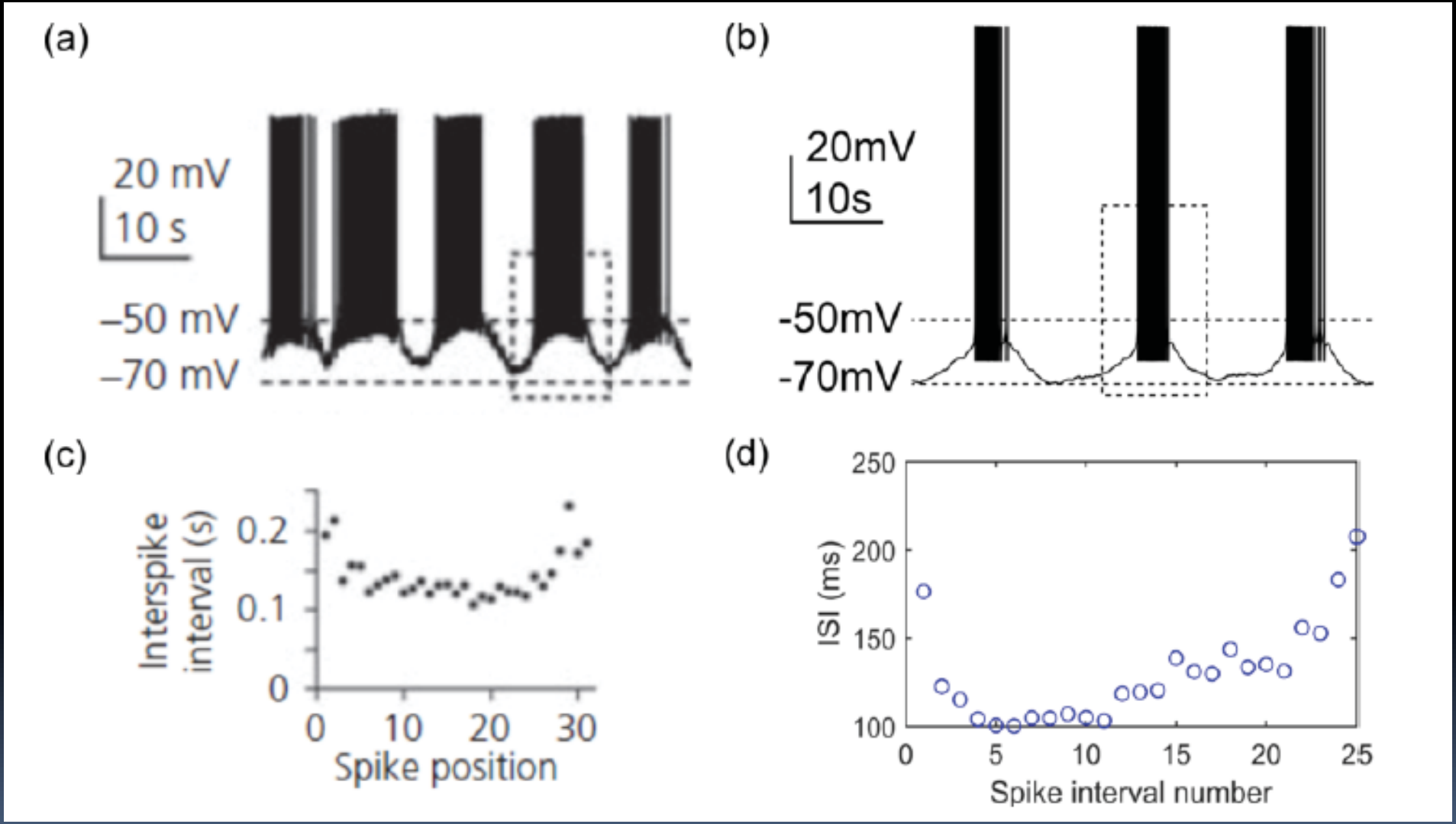


$$D(x) = \frac{1}{N}\sum_{i=1}^{N}\eta(x, y_i)$$

$$\eta(x, y) = \begin{cases} 0, & y \notin \Omega(x) \\ 1, & y \in \Omega(x) \end{cases},$$

$$E(x) = D_{model}(x) - D_{obs}(x).$$

Model simulations



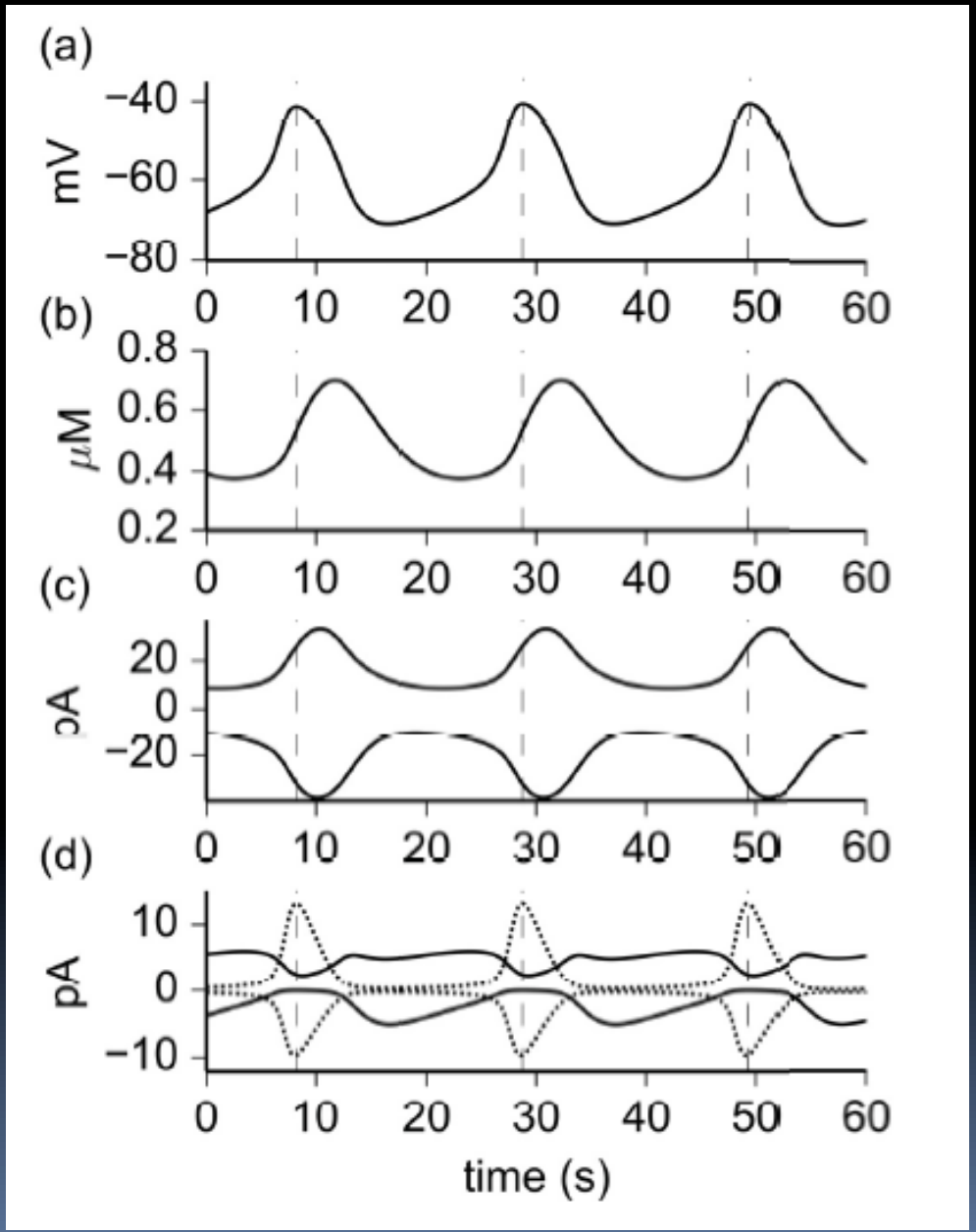
Model simulations

Voltage in the presence of TTX.

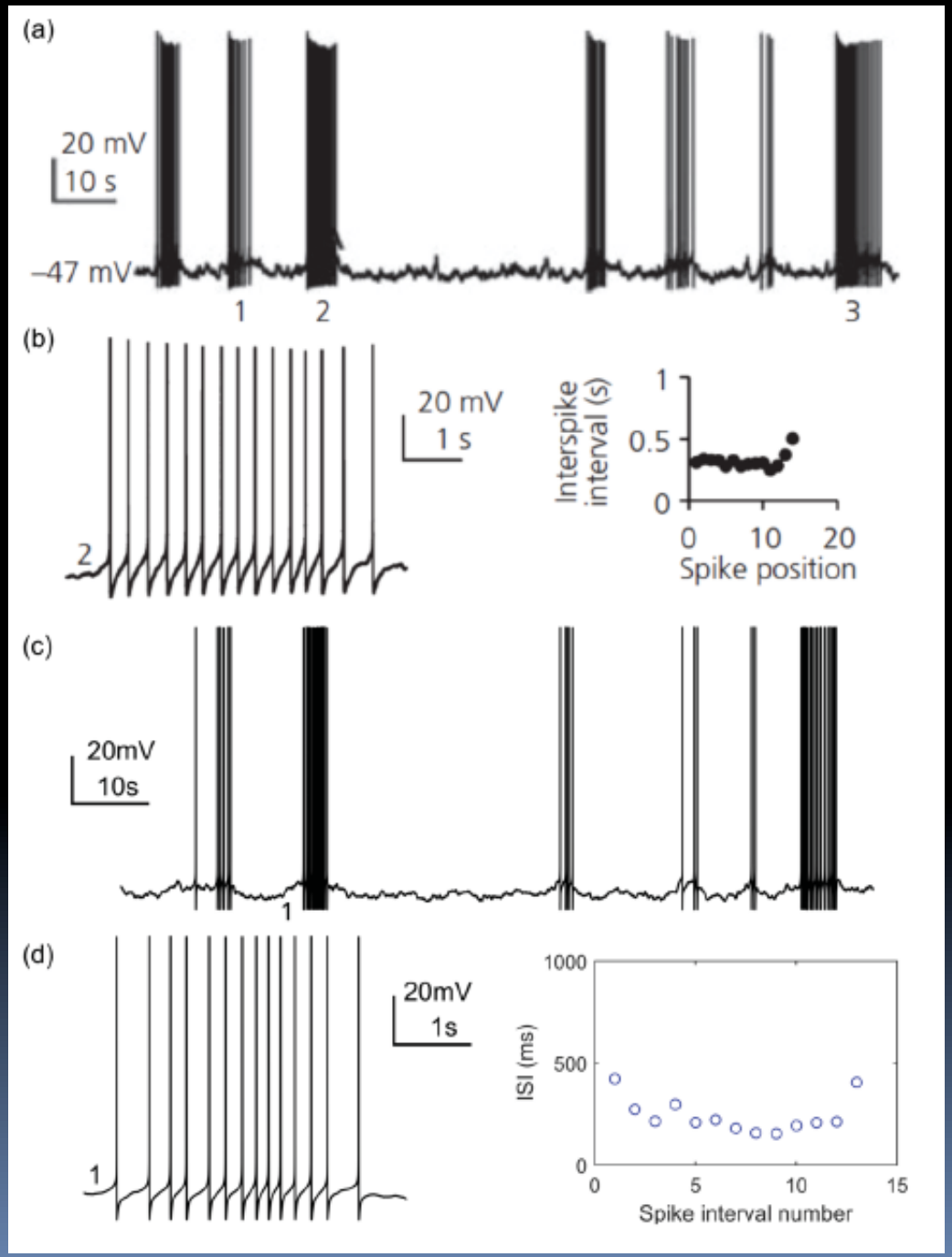
Calcium oscillations

I_s and $I_{K(Ca)}$

I_h, I_{HVA}, I_A and I_K

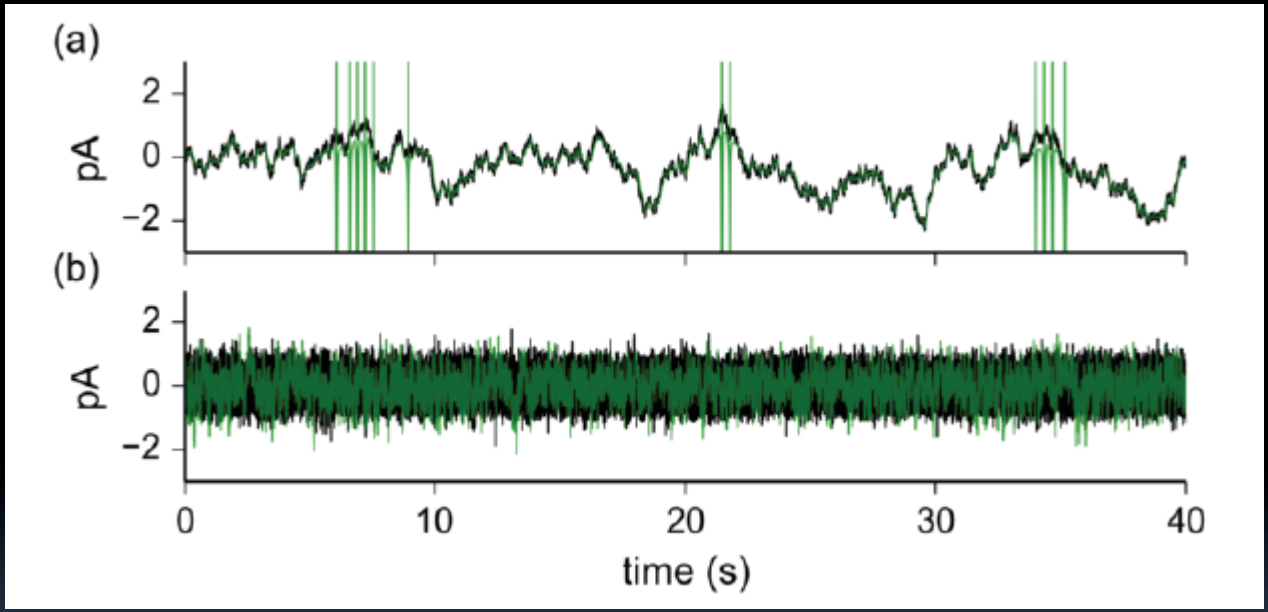


Model simulations



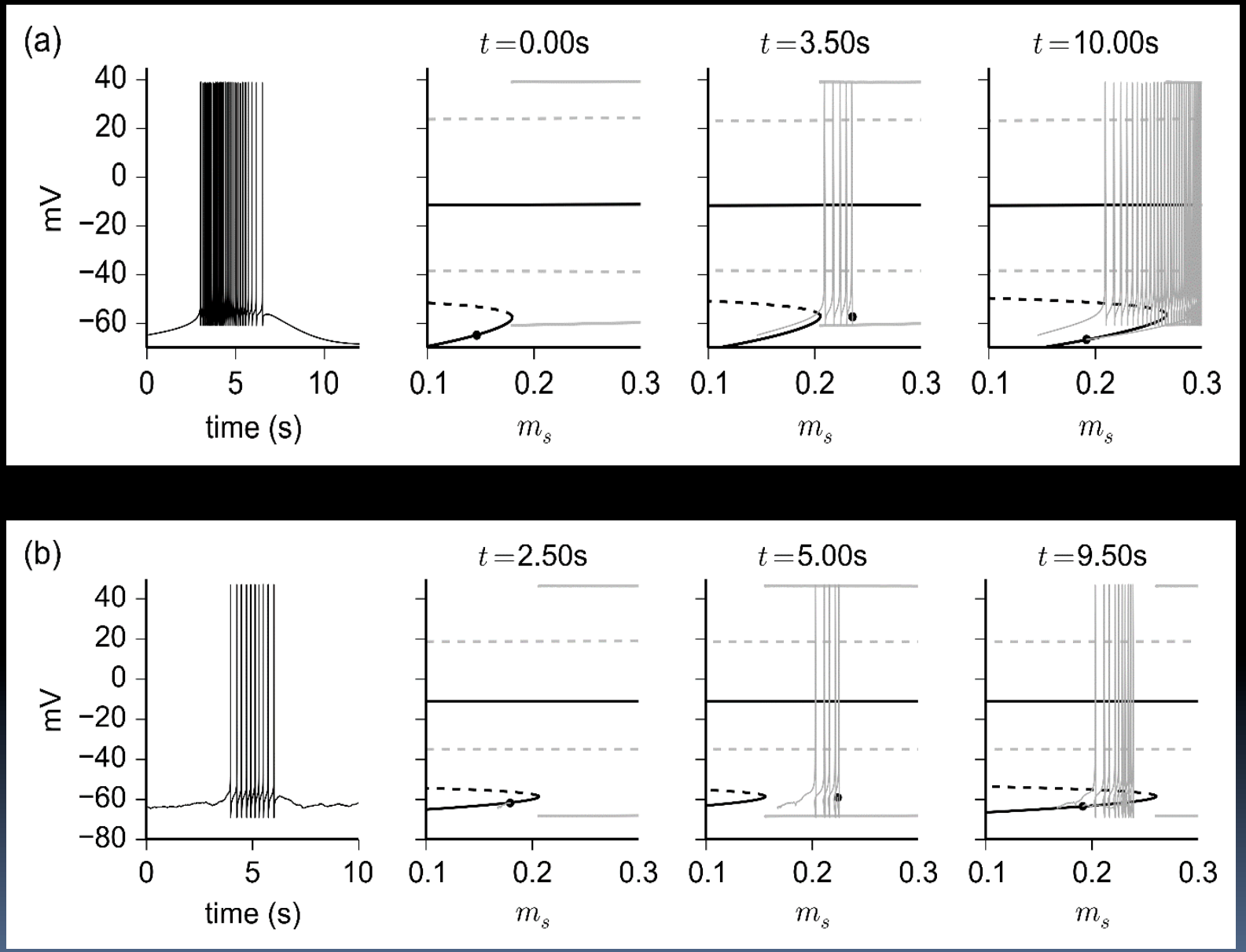
Noise (t_c, D)

The model exhibits a form of “stochastic resonance”.

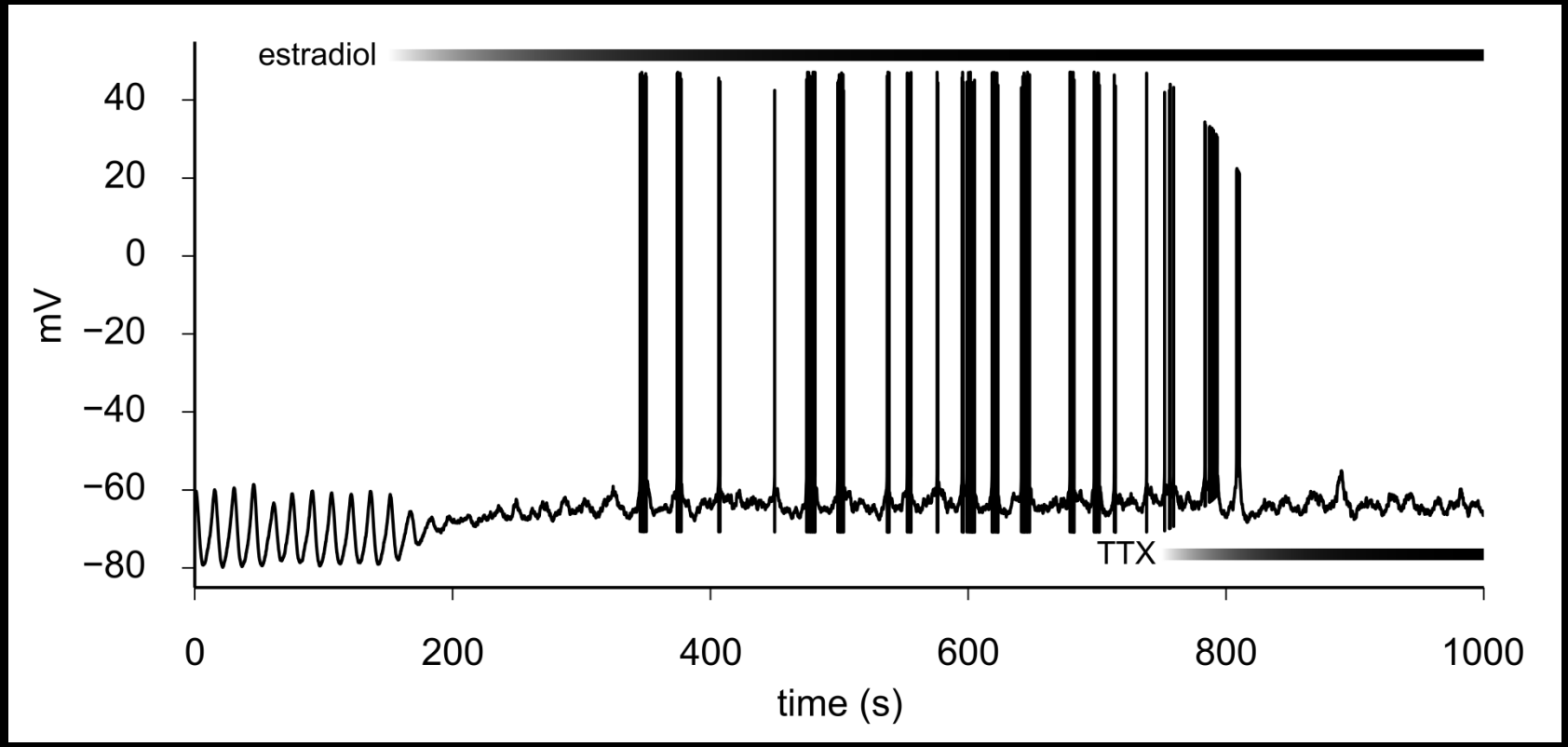


Slow-fast subsystem analysis

Three slow variables in This system: m_s, h_{HVA}, and Ca

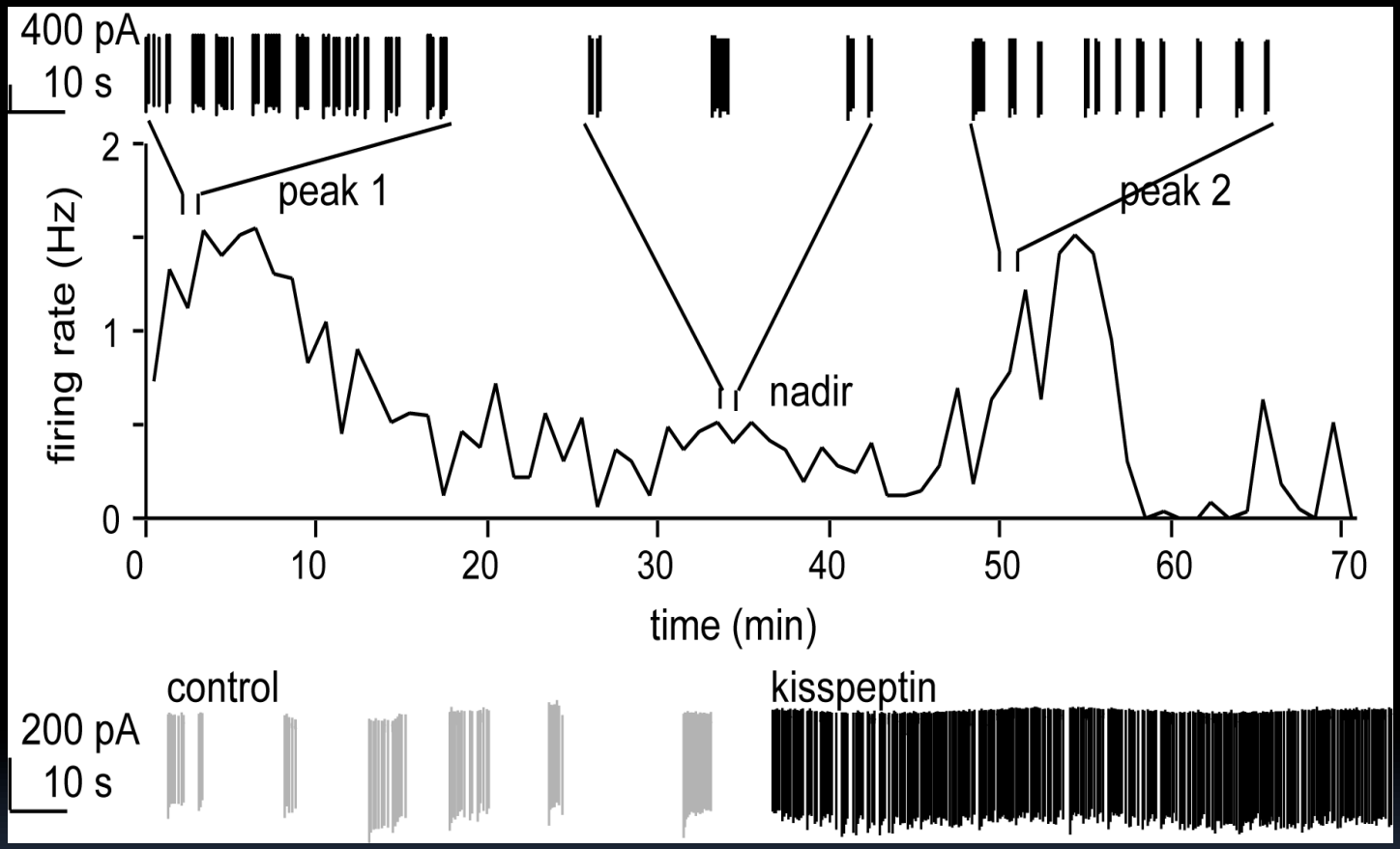


Effect of estradiol



Estradiol shifts parabolic bursters to irregular ones by decreasing the maximum conductances of I_s, $I_{K(Ca)}$, and I_A (to generate depolarized resting potential).

The big question



How is burst firing related to hormone release?

Conclusions

- GnRH neurons exhibit two modes of burst firing.
- HH-formalism can be used to explain the main differences between them.
- Parabolic and irregular bursters are topologically equivalent.
- Noise is key to bursting (must possess slow component).
- Estradiol affects three conductances: g_s, $g_{K(Ca)}$ and g_A.

Acknowledgment

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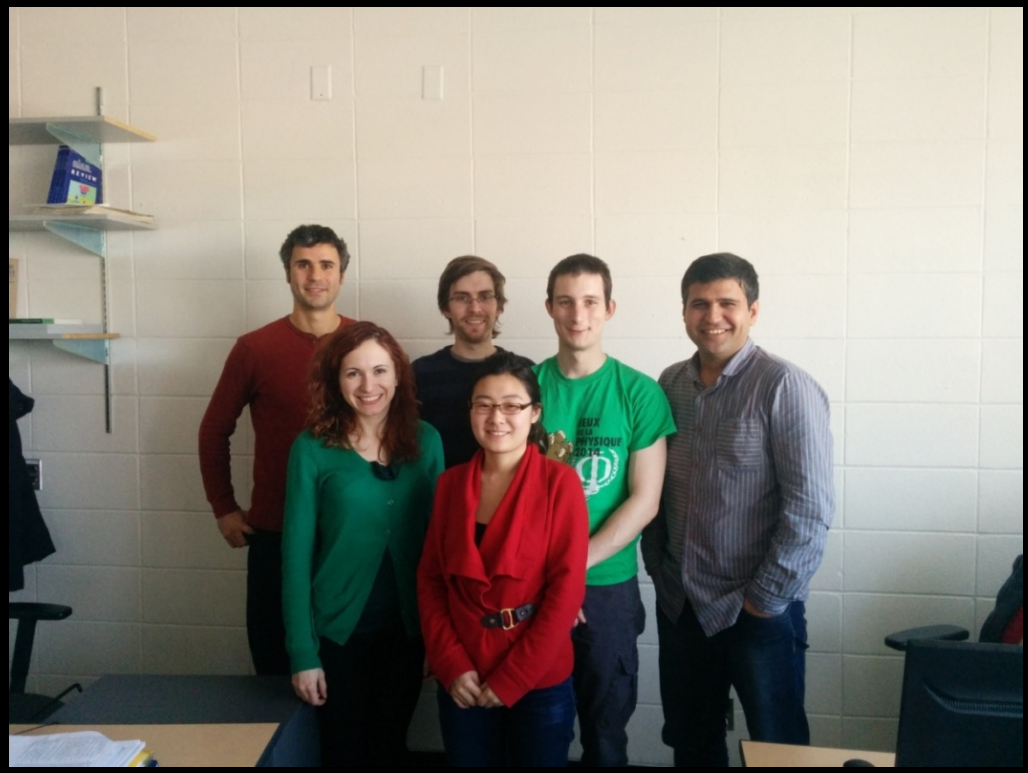

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