Modeling & simulating acupuncture

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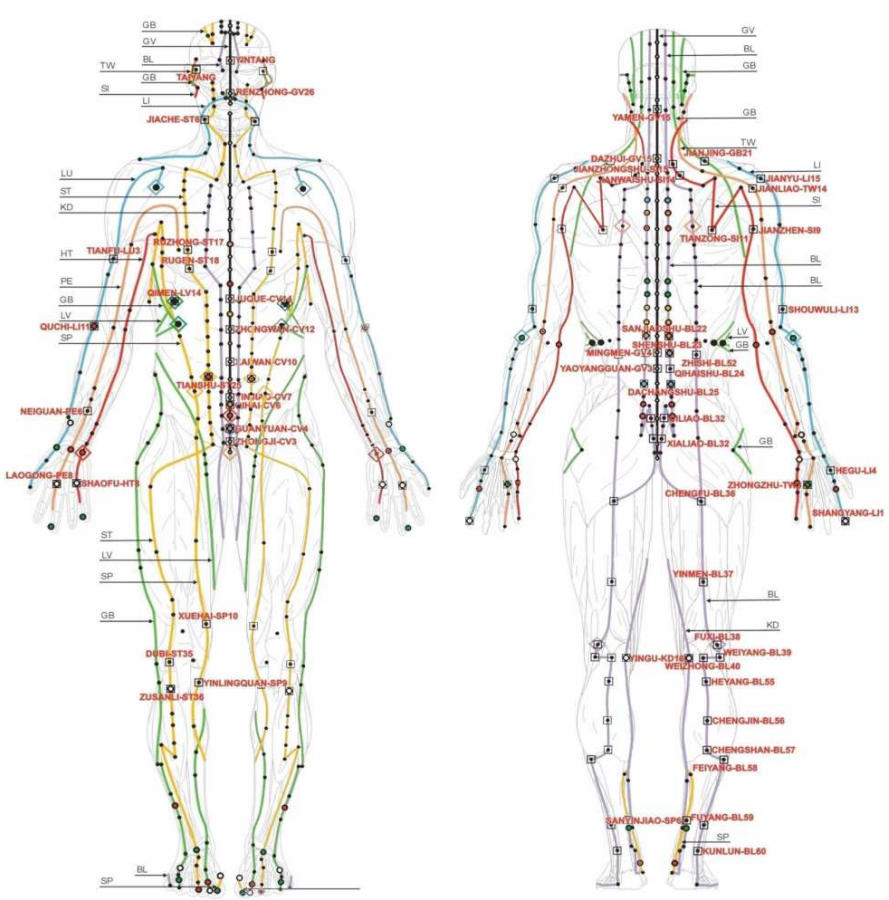
Acupuncture and Neurovascular Coupling!

Links by

1. **application**
   - Western anesthesia: coma-like state (irrelevant, used for the convenience of surgeons).
   - Acupuncture: appropriate + quick postoperative recovery + low cost health system (to be promoted)
     Brain: a wonderful chemical processor (natural analgesia &anesthesia)
2. **mode of operation**
   - signaling via nervous impulses and
   - signaling via endocrine messengers conveyed by blood flow
     They must cross BBB or more permeable capillary networks in neuroendocrine nuclei.

Meridians and Zang Fu Organs – Empirical knowledge



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12 main meridians

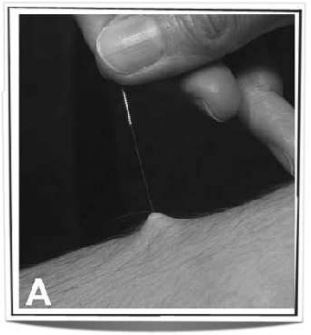
- 3 Yin meridians in hand
  - lung 肺
  - pericardium 心包
  - heart 心
- 3 Yang meridians in hand
  - large intestine 大腸
  - triple heater 三焦
  - small intestine 小腸
- 3 Yin meridians in foot
  - spleen 脾
  - liver 肝
  - kidney 腎
- 3 Yang meridians in foot
  - stomach 胃
  - gall bladder 膽
  - bladder 膀胱

+ extras meridians (collateral, superficial...)

2 comments

- maps drawn 2 millenaries ago;
- absence of a priori between-subject variability.

Acupuncture needling – Empirical knowledge



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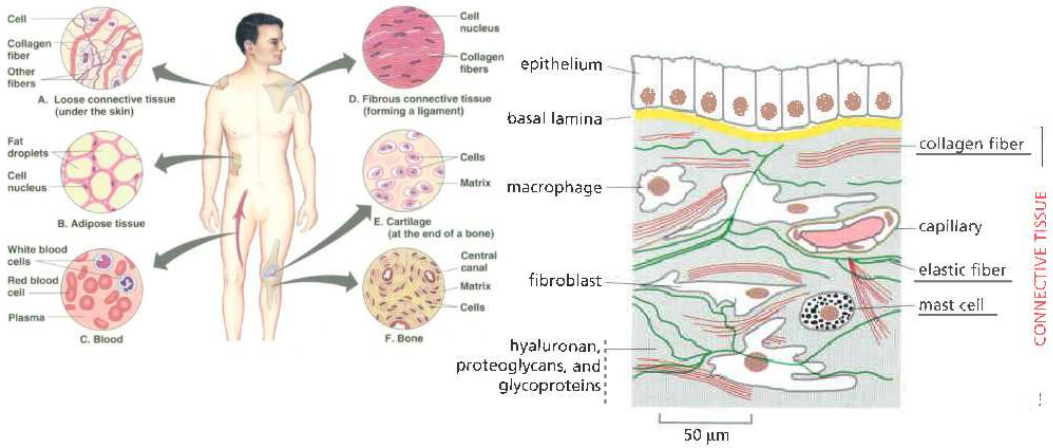


Bruce Alberts, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, Peter Walter. Molecular Biology of the Cell. 2008. Fifth Edition, Garland Science Publishers, New York.

Thin needles are implanted in the skin deep layer (hypodermis/subcutis) and used to deliver a local field of either a mechanical stress or a physical quantity (heat transfer or electrical field) or to stimulate photosensitive GPCRs.

Operating modes

- Long-term training to handle acupoints and become an expert
- 3 main techniques that can be combined
  1. development of a local mechanical stress field by needle motions (lifting–thrusting cycle or rotation) at acupoints (mechanotransduction);
  2. development of a local temperature field by directly applying a heating moxa (mugwort herb) stick on the skin or indirectly by applying this stick ot the acupuncture needle (moxibustion) at acupoints;
  3. development of a local electrical field by applying a small electric current between a pair of acupuncture needles (electroacupuncture, or percutaneous electrical nerve stimulation [PENS]) at acupoints.
  4. stimulation of photosensitive GPCRs by laser light at acupoints in the absence of physical effects.

Regimes

1. **Transient**: puncture (rapid penetration of needle through the skin)
2. **Stable**: needle tip has reached the wanted position and stmulation has ceased.

Transient regime —puncturing; development of a mechanical stress field
Poroviscoelasticity (Biot model or extended FSI-associated Brinkman model)
normal and tangential stress on the cell surface—mechanotransduction

Steady regime —needle insertion in deep subcutaneous loose connective tissue
stable sustained deformed conformation (ball of radius 5 mm)

Strain and Stress

Puncturing-associated forces and resulting deformations exerted on:

- interstitial fluid (water + ions + small molecules = plasma − large molecules [constrained Stokes flow]);
- ground substance (glyco*proteins* and proteo*glycans* [MPS–proteins]) – gel-like medium;
- multiple layers of thin collagen sheets loosely interconnected by elastin fibers;
- cells (fibroblasts, fibrocytes, and immunocytes); and
- neurovascular bundles

Acupoint

- large density of mastocytes;
- close to neurovascular bundles;
- great capillary density;
- not far from bones, aponeuroses, muscles, and/or tendons;
- large skin electrical conductance;
- high ionic concentrations
  (K^{+}, Ca^{++}, Fe^{++}, Mn^{++}, Zn^{++}, PO_4^{3-}).

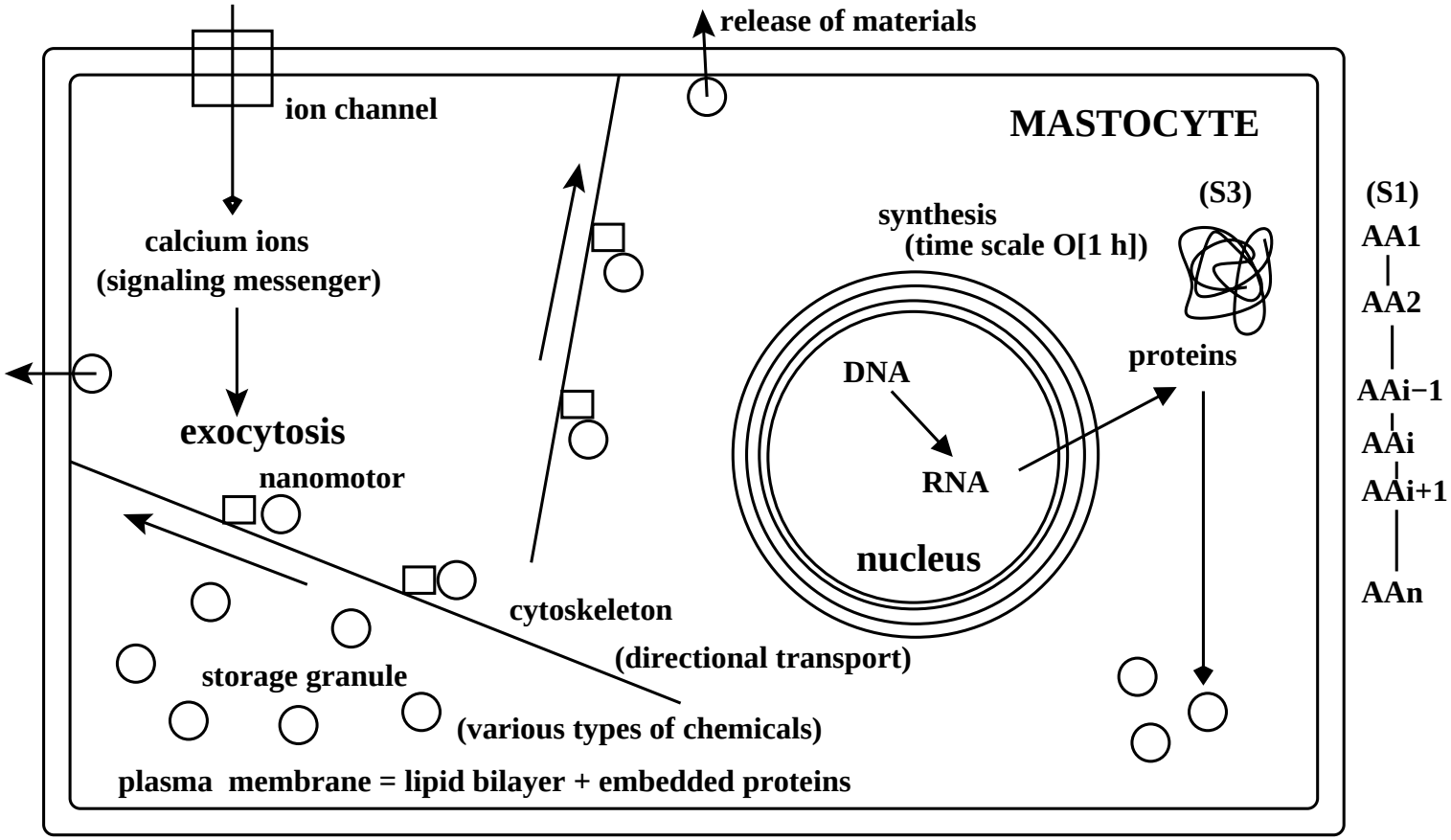
Mastocyte

immunocyte that

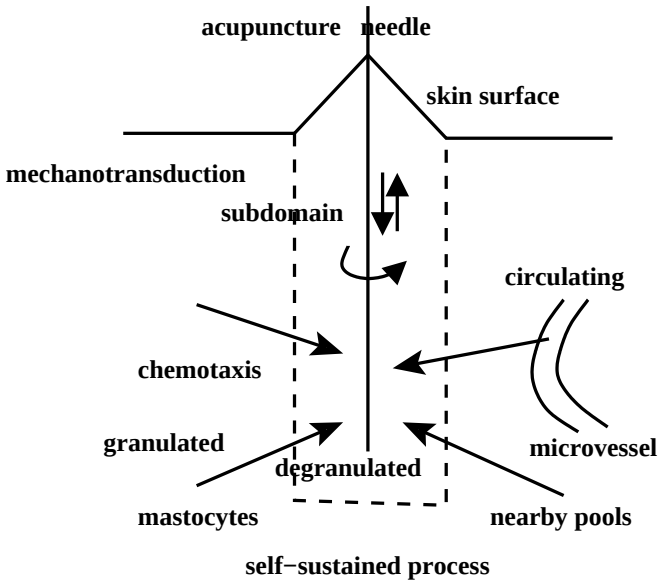
- contains granules storing chemical mediators
- release granule content within minutes for intra-, auto-, juxta-, para-, and endocrine signaling.

recruitment to acupoints — **chemotaxis**
self-sustained process that enables continuous secretion of messengers by arrivals of new mastocyte pools from nearby capillaries and regional mastocyte populations

Mastocyte response to physical stimuli – Ca^{2+} influx & degranulation



Chemotaxis of circulating and tissular mastocytes



1. transmigration of circulating mastocytes (across blood vessel walls, i.e., exit from blood)
2. migration of loaded (granulated) mastocytes across a region of low-amplitude mechanical stress [threshold ℓ])
3. migration across a region of triggering mechanical stress and unloading (degranulation) [close to needle: 0—ℓ]

Adjoining and remote targets

Nerve terminals
- immediate triggering (O[1 s–1mn]) of fast, short-lived action potentials, but sustained action due to cell recruitment;
- hyperemia in a given local brain region (attractor for endocrine messengers);
- neurotransmission using endocannabinoids, antalgics, etc.

Capillaries
- increase in permeability (enhanced transport)
- blood and lymph convection of endocrine messengers to the brain
- delayed, slower, but sustained (because of cell recruitment)

Heart increase in blood flow rate

Brain wanted afferent signaling

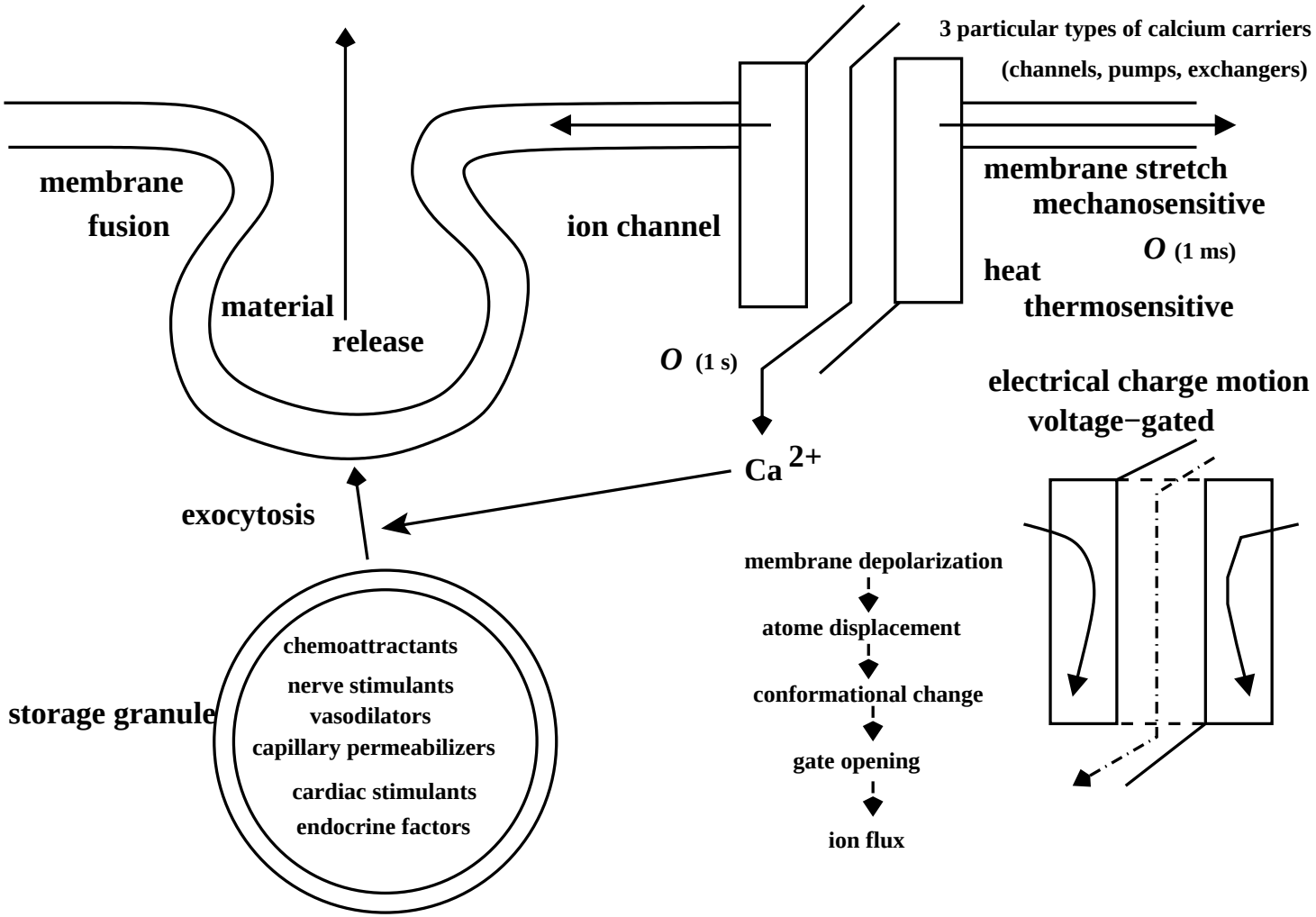
Cell responses to a physical field

- Mastocyte stimulation by a physical process opens calcium ion channel;
- Cytosolic Ca^{2+} causes granule transport to the cell surface and liberation of content

activated ion channel	$\mathcal{O}(\text{ms})$
$[\text{Ca}^{2+}]_\text{i}$	$\mathcal{O}(\text{s})$

1. mechanosensitive Ca^{2+} channel
2. thermosensitive Ca^{2+} channel
3. voltage-gated Ca^{2+} channel
4. Ca^{2+} channel coupled with photosensitive GPCRs

Calcium ion channel gating



Released substances

Agent	Effects
CGRP	Vasodilation, positive chronotropy, inotropy, and lusitropy, mastocyte degranulation
Heparin	Blood clot prevention
Histamine	Vasodilation (directly and via NO), nerve stimulation
Leukotrienes	Vasodilation, vascular permeability elevation
IL, NGF, TNF	Chemotaxis
Prostaglandin-D2	Nerve stimulation
Prostaglandin-E2	Vasodilation, inhibition of mediator release
Serotonin	Vasoconstriction followed by NO-mediated vasodilation
Thromboxane-A2	Vasoconstriction, platelet aggregation
Tryptase, chymase	Matrix degradation for enhanced cell migration

Summary of effects

- generation of a local stress field
- mechanotransduction (Ca^{2+} entry, granule exocytosis, substance release)
- triggering of action potential (early, quick response)
- chemotaxis (from regional pools and blood)
- degranulation of newly arrived mastocytes at acupoints (autosustained process)
- local elevation of vascular permeability for enhanced endocrine signaling and improved cardiac output
- vasodilation with increased blood flow (cardiac effect)
- delayed, permanent endocrine signaling to CNS (preferential distribution in hyperemic region)

Data & hypotheses

- Relatively high density of resting mastocytes at acupuncts;
- 2 mastocyte states according to localization w.r.t. acupoint: non-degranulated and degranulated;
- Quasi-instantaneous release of chemical mediators upon stimulation (mechanotransduction & calcium influx);
- release of chemoattractants, nerve messengers, cardiovascular stimulants, and endocrine messengers;
- delayed regeneration of granules content,
- negligible convection (Stokes flow) in the matrix

Variables and Parameters

For $x \in \Omega$ bounded and $t \in \mathbb{R}^+$:

- $n_g(t,x)$: density of granulated mastocytes
- $n_d(t,x)$: density of degranulated mastocytes
- $c(t,x)$: concentration of chemoattractant
- $s_n(t,x)$: concentration of nerve stimulant
- $s_e(t,x)$: concentration of endocrine stimulant

equation related to granulated mastocytes

equation related to the pool of degranulated mastocytes

equation related to chemoattractant

equation related to nervous messenger

equation related to endocrine messenger

Biomathematical model

mastocyte/chemoattractant/nervous messenger/endocrine mediator

$$
\begin{aligned}
\partial_t n_g - \mathcal{D}_m \nabla^2 n_g + \nabla \cdot (\mathrm{S}\, n_g \nabla c) &= -\mathrm{A}\Phi n_g + \mathrm{R} n_d; \quad (1)\\
\partial_t n_d - \mathcal{D}_m \nabla^2 n_d &= \mathrm{A}\Phi n_g - \mathrm{R} n_d; \quad (2)\\
\partial_t c - \mathcal{D}_c \nabla^2 c &= \kappa_c \mathrm{A}\Phi n_g - \mathrm{D}_c c; \quad (3)\\
\partial_t s_n - \mathcal{D}_n \nabla^2 s_n &= \kappa_n \mathrm{A}\Phi n_g - \mathrm{D}_n s_n; \quad (4)\\
\partial_t s_e - \mathcal{D}_e \nabla^2 s_e &= \kappa_e \mathrm{A}\Phi n_g - \mathrm{D}_e s_e; \quad (5)\\
t > 0; \quad \mathbf{x} \in \Omega.
\end{aligned}
$$

- $\Phi(x)$: magnitude of mechanical stress $0 \leq \Phi(x) \leq 1$ $(0 \leq \mathbf{x} \leq \ell)$;
- $\mathcal{D}_{m/c/n/e}$: diffusion coefficient $[\mathrm{L}^2\mathrm{T}^{-1}]$;
- A: activation rate $[\mathrm{T}^{-1}]$;
- R: regeneration rate of degranulated masotocytes $[\mathrm{T}^{-1}]$;
- S: mastocyte sensitivity to chemoattractant $([\mathrm{L}^4\mathrm{mol}^{-1}\mathrm{T}^{-1}])$;
- $\kappa_{c,e,n}$: release quantity coefficient [mol].

equations physically homogeneous

Simplified model for analytical solution

in the absence of evolving (in time) chemoattractant concentration,

$$\begin{aligned} \partial_t n - \nabla^2 n + \nabla \cdot (\mathsf{S} n \nabla c) &= -\mathsf{A}\Phi n; \\ -\mathcal{D}_c \nabla^2 c &= \kappa_c \mathsf{A}\Phi n; \\ n_{t=0} &= n_0 \geq 0; \\ t > 0; \quad \mathbf{x} \in \mathbb{R}^2. & \end{aligned}$$

distribution analysis – moments
(mean, variance, skewness, kurtosis, etc.)

cell concentration around the needle — acupoint *vs.* common mastocyte pool

Theorem

a singularity appears in a finite time and the cell density blows up at the singularity point, if

- $m_0 := \int_{\mathbb{R}^2} n_{nd}^0 > \frac{8\pi}{LS_{ca}}$,
- $\int_{\mathbb{R}^2} |x^2| n_{nd}^0(x) dx \leq \xi^*$,

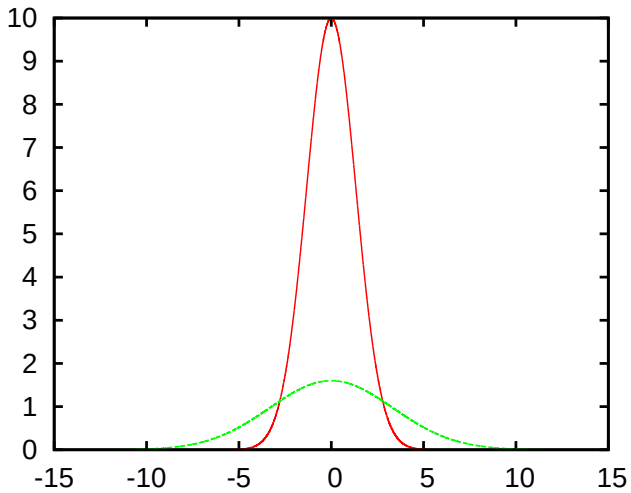
with

$$\xi^* = \frac{1}{4}\left[\frac{3(m_0)^{\frac{1}{2}}}{k_\phi}\sqrt{1 + L\frac{k_\phi}{m_0}\left(m_0 - \frac{8\pi}{LS_{ca}}\right)} - 1\right]^2. \qquad (6)$$

Blow-up of the solution if:

- the initial density of mastocytes is high enough;
- the second moment is small enough (small dispersion).

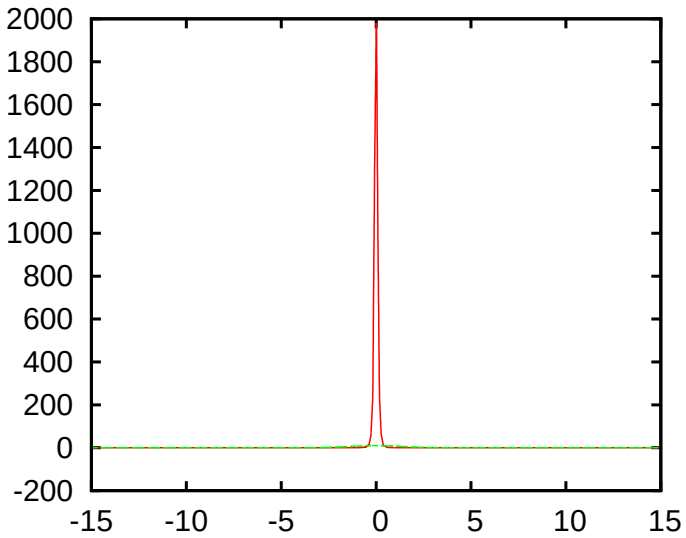
Results

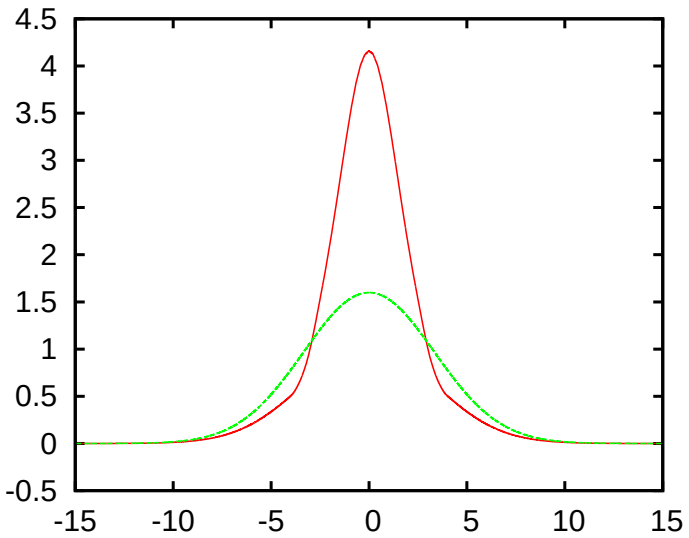


Initial mastocyte Gaussian distribution (same cell number):

- acupoint (concentrated distribution; $m_0(0) = 50$, $m_2(0) = 11.12$)
- non-acupoint (dispersed distribution; $m_0(0) = 50$, $m_2(0) = 165.19$)

Results





different axis magnitude

blow up (efficiency) *vs.* mild response

Temporary end of the story

variable modeling outcomes, *i.e.*,

- capacity of a model to explain, describe, and predict, and
- its level of applicability to daily practice and training

THANK YOU FOR YOUR ATTENTION