

Summary of DART ISN project

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1 Dart paradoxical effect with locomotion

To quantitatively investigate why the dart paradoxical effect occurs, we used a three population rate model (Sanzeni et al., 2020) in which the average firing rates of pyramidal (r_e), parvalbumin (r_p) and somatostatin (r_s) cells evolve according to:

$$\tau_e \frac{dr_e}{dt} = -r_e + \Phi(W_{ee}r_e - W_{ep}r_p - W_{es}r_s + I_{ex})$$

$$\tau_p \frac{dr_p}{dt} = -r_p + \Phi(W_{pe}r_e - W_{pp}r_p - W_{ps}r_s + I_{px})$$

$$\tau_s \frac{dr_s}{dt} = -r_s + \Phi(W_{se}r_e)$$

Where τ_A is the time constant for the population A, I_Ax is the external excitation to the population A, W_{AB} is the strength of connections from population B to A. W_{ss} and W_{sp} have empirically been shown to be relatively negligible (Pfeffer et al., 2013), which is why these weights are omitted here. Because there are no direct connections from the LGN to V1 SST cells, and because SST cells have weak spontaneous responses, we here assume that $I_{sx} = 0$. Results from the simulations have been obtained with a rectified-linear transfer function where:

$$\Phi(x) = a_A[x - x_{0A}]_+$$

which is 0 for input x smaller than the threshold x_{0A} , and increases linearly with a gain a_A otherwise. For the purpose of this work, x_{0A} have all been set to 0 and a_A have all been set to 1. In the mathematical proof results, the transfer function was simply linear where:

$$\Phi(x) = x$$

Because the firing rate regime of neurons is usually significantly above 0, these two transfer functions usually gave similar results. Assuming a linear transfer function, the steady-state solutions ($\frac{dr_e}{dt} = 0$, $\frac{dr_p}{dt} = 0$, $\frac{dr_s}{dt} = 0$) of the set of differential equations mentioned above are:

$$r_e = W_{ee}r_e - W_{ep}r_p - W_{es}r_s + I_{ex}$$

$$r_p = W_{pe}r_e - W_{pp}r_p - W_{ps}r_s + I_{px}$$

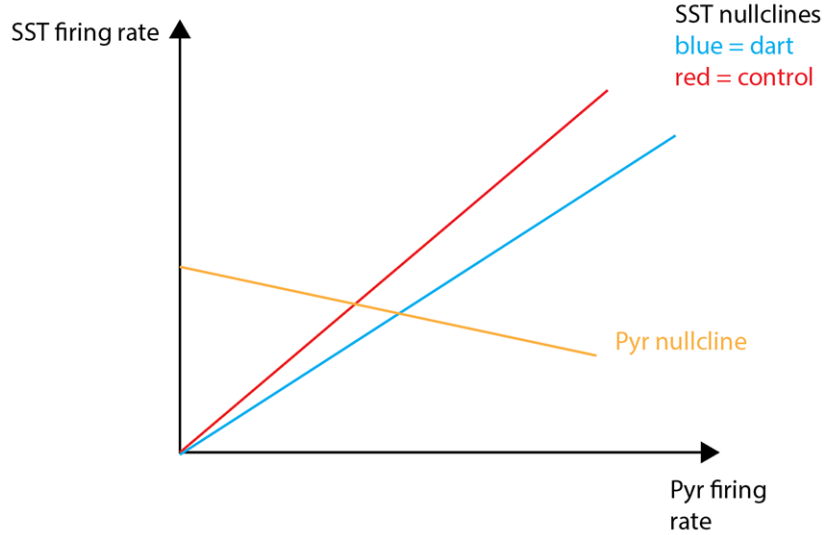
$$r_s = W_{se}r_e$$

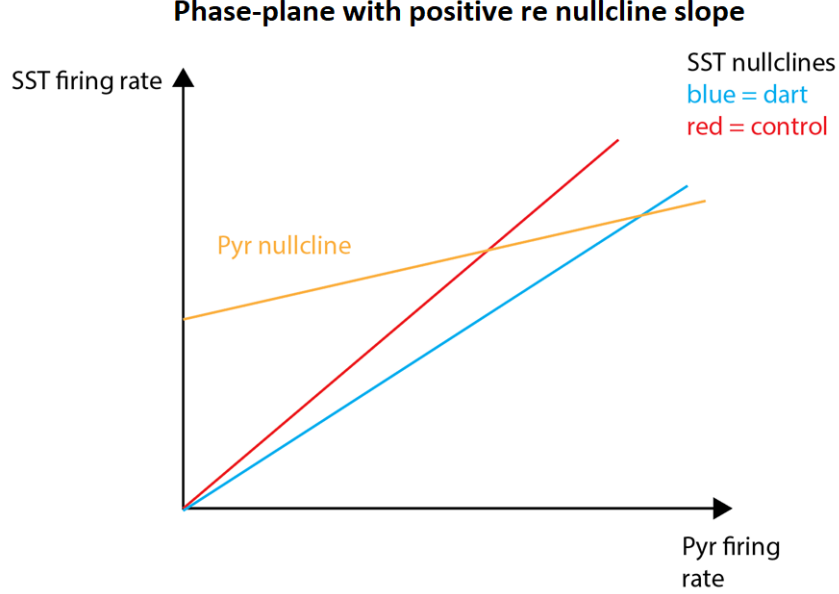
To perform the phase-plane analysis, we inferred the r_s and r_e nullclines. If we assume that DART is a non-competitive antagonist, then the r_s nullcline is simply $r_s = dW_{se}r_e$, where $0 \leq d \leq 1$ represents the strength of the DART antagonist. The r_e nullcline has been shown to be the following:

$$r_s = r_e \frac{-\det(I - W_2)}{W_{es}(W_{pp} + 1) - W_{ep}W_{ps}} + \frac{I_{ex}(W_{pp} + 1) - W_{ep}I_{px}}{W_{es}(W_{pp} + 1) - W_{ep}W_{ps}}$$

Where $\det(I - W_2) = -W_{ee}W_{pp} - W_{ep}W_{pe} - W_{ee} + W_{pp} + 1$. The detailed proof for the r_e nullcline can be found in the Supplementary below. As is visually shown below, it turns out whether DART increases or decreases the responses of SST cells depends on whether the slope of the r_e nullcline is positive or negative

Phase-plane with negative r_e nullcline slope





As shown above, the slope of the r_e nullcline is determined by $\frac{-\det(I-W_2)}{W_{es}(W_{pp}+1)-W_{ep}W_{ps}}$. According to the connectivity matrix from Pfeffer et al. (2013), the denominator $W_{es}(W_{pp}+1)-W_{ep}W_{ps}$ should be negative. This is somewhat intuitive, since direct inhibition of Pyr cells by SST cells (W_{es}) should be stronger than the disinhibitory effect of Pyr by SST through PV cells ($W_{ep}W_{ps}$).

However, whether $\det(I-W_2)$ is negative or positive is less clear. Its important to keep in mind that the units reported in Pfeffer et al. (2013) are somewhat arbitrary, and the same 'connectivity' is conserved if we multiply every weight by a constant g . As is shown in the next section, if $\det(W_2) < 0$, then $\det(I-W_2) < 0$ as g increases towards ∞ and $\det(I-W_2) > 0$ as g decreases towards 0.

2 Slope of the r_e nullcline

Next, I will try to explain why $\det(I-W_2)$ can go from positive to negative by multiplying W_2 by a positive constant g .

We can rewrite $0 > \det(I-W_2)$ as:

$$-W_{ee}W_{pp} + W_{ep}W_{pe} - W_{ee} + W_{pp} < -1$$

If we multiply every weight (e.g. W_{ee} , W_{pp} ...) by a positive constant g , the above inequality becomes:

$$-W_{ee}W_{pp} + W_{ep}W_{pe} < \frac{W_{ee} - W_{pp} - \frac{1}{g}}{g}$$

Let's take a closer look at the limits of $\frac{W_{ee} - W_{pp} - \frac{1}{g}}{g}$:

$$\lim_{g \rightarrow 0} \frac{W_{ee} - W_{pp} - \frac{1}{g}}{g} = -\infty$$

$$\lim_{g \rightarrow \infty} \frac{W_{ee} - W_{pp} - \frac{1}{g}}{g} = 0$$

This tells us two important pieces of information:

1. $\det(I - W_2) > 0$ as g tends towards 0.
2. If $\det(W_2) < 0$, then $\det(I - W_2) < 0$ as g increases towards ∞ .

Interestingly, $\det(I - W_2) = 0$ when $g = \frac{a_1}{\det(W_2)}$ or $g = \frac{a_2}{\det(W_2)}$. a_1 and a_2 are the two eigenvalues of the matrix W_2 :

$$a_1 = \frac{W_{ee}}{2} - \frac{W_{pp}}{2} - \frac{\sqrt{W_{ee}^2 + 2W_{ee}W_{pp} - 4W_{ep}W_{pe} + W_{pp}^2}}{2}$$

$$a_2 = \frac{W_{ee}}{2} - \frac{W_{pp}}{2} + \frac{\sqrt{W_{ee}^2 + 2W_{ee}W_{pp} - 4W_{ep}W_{pe} + W_{pp}^2}}{2}$$

For the connectivity matrix W_2 from Pfeffer et al. (2013), $\det(W_2) < 0$, $\frac{a_1}{\det(W_2)} \approx 0.99$ and $\frac{a_2}{\det(W_2)} \approx -50.5$.

Because g can only take positive values, we get the paradoxical effect from DART when $g > 0.99$. Therefore, if we assume that locomotion were to increase the gain of neurons by a constant g , this would explain why we go from DART decreasing SST firing rate when the animal is stationary to increasing SST firing rate when the animal is running.

In theory, the same argument could also be applied to the denominator of the r_e nullcline slope $W_{es}(W_{pp} + 1) - W_{ep}W_{ps}$. However, this denominator can only become negative as g increases if $W_{es}W_{pp} < W_{ep}W_{ps}$, which isn't the case in the weights from Pfeffer et al. (2013).

3 Modeling DART as a competitive antagonist

So far we've assumed that dart is a non-competitive antagonist, and that we can model it by multiplying $W_{se}r_e$ by a constant d that varies from 0 to 1. The slope of the r_s nullclines is linear, and the slope diminishes as you increase the effect of dart. This simple non-competitive DART model implies that as we increase contrast (i.e. I_{ex} and I_{px} , or the intercept of the r_e nullcline), then the effect of DART should increase. However, this is not what is experimentally observed; as we increase contrast, the difference in SST responses between DART and control conditions remain relatively constant.

To address this question, here we model DART as a competitive antagonist and compute the corresponding r_s nullcline. As is shown below, a competitive antagonist model would explain why the effect of DART remains relatively constant across different contrast levels.

Let's find the nullcline of r_s for a competitive DART antagonist to better understand why the effect of DART remains relatively constant across contrasts.

Competitive antagonists have been modeled as follow (Heuvel, 2010):

$$\frac{\Delta}{\Delta_{max}} = \frac{a}{a + K_d(1 + \frac{1}{K_I})}$$

Where $\frac{\Delta}{\Delta_{max}}$ is the response with antagonist divided by the response without antagonist and a is the agonist concentration. K_d and K_I are dissociation constants. For our purpose, we can simplify the above formula by defining $d = K_d(1 + \frac{1}{K_I})$, where d is a function of how potent the DART antagonist is. The above formula then becomes:

$$\frac{\Delta}{\Delta_{max}} = \frac{a}{a + d}$$

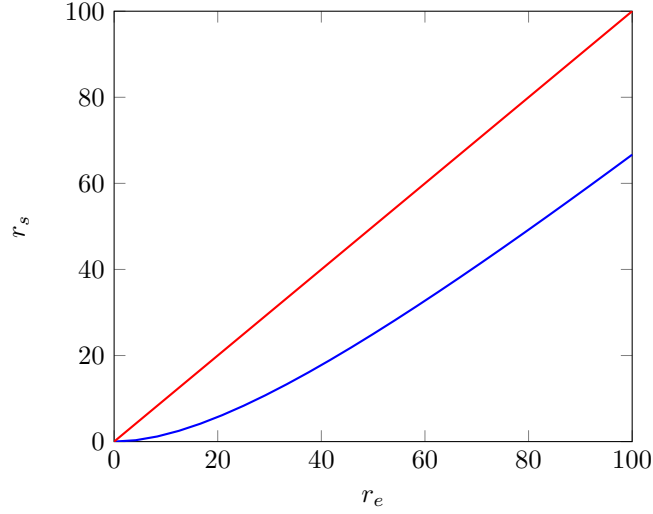
In the present scenario, $a = W_{se}r_e$, which is the amount of glutamate received by AMPA receptors on SST cells. To model the competitive effect of DART, we can multiply $W_{se}r_e$ by $\frac{\Delta}{\Delta_{max}}$, the proportion of the maximum response with and without the antagonist. The steady-state responses for the Pyr-PV-SST system then becomes:

$$r_e = W_{ee}r_e - W_{ep}r_p - W_{es}r_s + I_{ex}$$

$$r_p = W_{pe}r_e - W_{pp}r_p - W_{ps}r_s + I_{px}$$

$$r_s = \frac{(W_{se}r_e)^2}{W_{se}r_e + d}$$

As we can see below, the slopes of the two r_s nullclines are more or less parallel for $x \in [40, \infty]$. These parallel nullclines would help explain some of the experimental findings from Celine; more specifically, it would help explain why the difference in SST responses for the control and DART conditions stays relatively constant across different contrasts.



4 Supplementary - re nullcline proof

In a three population network, the steady state equations ($\frac{\partial r_e}{\partial t} = 0$, $\frac{\partial r_p}{\partial t} = 0$, $\frac{\partial r_s}{\partial t} = 0$) are as follow (Pfeffer et al., 2013) :

$$r_e = W_{ee}r_e - W_{ep}r_p - W_{es}r_s + I_{ex}$$

$$r_p = W_{pe}r_e - W_{pp}r_p - W_{ps}r_s + I_{px}$$

$$r_s = W_{se}r_e + I_{sx}$$

To study the nullcline for r_e , let's first isolate r_p :

$$r_p = \frac{W_{pe}r_e - W_{ps}r_s + I_{px}}{W_{pp} + 1}$$

We can then express r_e as a function of r_s without r_p :

$$\begin{aligned} r_e &= W_{ee}r_e - W_{ep} \frac{W_{pe}r_e - W_{ps}r_s + I_{px}}{W_{pp} + 1} - W_{es}r_s + I_{ex} \\ r_e \left(1 + \frac{W_{ep}W_{pe}}{W_{pp} + 1} - W_{ee}\right) &= -W_{ep} \frac{-W_{ps}r_s + I_{px}}{W_{pp} + 1} - W_{es}r_s + I_{ex} \\ r_e &= \frac{-W_{ep} \frac{-W_{ps}r_s + I_{px}}{W_{pp} + 1} - W_{es}r_s + I_{ex}}{\left(1 + \frac{W_{ep}W_{pe}}{W_{pp} + 1} - W_{ee}\right)} \end{aligned}$$

If we multiply both the numerator and denominator by $W_{pp} + 1$:

$$r_e = \frac{-W_{ep}(-W_{ps}r_s + I_{px}) + (W_{pp} + 1)(-W_{es}r_s + I_{ex})}{W_{pp} + 1 + W_{ep}W_{pe} - W_{ee}(W_{pp} + 1)}$$

Let's isolate r_s . Let's also replace the denominator by $\det(I - W_2) = -W_{ee}W_{pp} - W_{ee} + W_{pp} + W_{ep}W_{pe} + 1$:

$$r_e = r_s \frac{W_{ep}W_{ps} - W_{es}(W_{pp} + 1)}{\det(I - W_2)} + \frac{I_{ex}(W_{pp} + 1) - W_{ep}I_{px}}{\det(I - W_2)}$$

Therefore, the slope of the r_e nullcline relative to r_s is :

$$\frac{W_{ep}W_{ps} - W_{es}(W_{pp} + 1)}{\det(I - W_2)}$$

If this slope of the r_e nullcline is negative, then the intersection of the two nullclines should happen at a lower r_s as we decrease W_{se} (the slope of the r_s nullcline). If the slope of the r_e nullcline is positive, then the intersection should occur at a higher r_s as we decrease W_{se} .