# Doggett et al. (2003) — "Alterations in the intrinsic properties of the GPIb$\alpha$-vWF tether bond define the kinetics of the platelet-type von Willebrand disease mutation, Gly233Val"

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## 1 Introduction

In their previous paper, Doggett et al compared the kinetic properties of the GP1b-vWF bond with wild type vWF and with 2B mutated vWF Doggett et al. (2002). In this paper, they study adhesion of platelets donated from patients with Platelet-type von Willebrand disease (PT-vWD). These patients are heterozygous for a mutation in the GP1b receptors, therefore theirpa platelets have both wild-type and mutant GP1b receptors. The authors developed three hypothetical models of platelet binding to account for this heterogeneous population of GP1b:

1. All tethering events are mediated by a single mutant GP1b-vWF bond.

2. All tethering events are mediated by a single GP1b-vWF bond, which can either be wild-type or mutant.

3. Tethering can be mediated by multiple GP1b-vWF bonds of either type.

## 2 Models

In Model 1, the pause time represents the length of time it takes for a single mutant GP1b and vWF to dissociate. Assume dissociation is a 1st order reaction with rate $k_{off,\ mut}$. Then the pause times are exponentially distributed with $\langle t\rangle = 1/k_{off,\ mut}$ (i.e. $P(t) = k_{off,\ mut}\exp(-k_{off,\ mut}t)$). For this model, the statistical estimate of $k_{off,\ mut}$ is simply $k_{off,\ mut} = 1/\langle t\rangle$.

For Model 2, a fraction $q$ of GP1b-vWF bonds are with wild-type GP1b and $1-q$ of GP1b-vWF bonds are with mutant GP1b. The pause time represents the length of time it takes one of these bonds to dissociate, and if we assume first-order kinetics for both of these bonds, then the pause time distribution is given by $P(t) = qk_{off,\ wt}\exp(-k_{off,\ wt}t) + (1-q)k_{off,\ mut}\exp(-k_{off,\ mut}t)$. Aside: the parameter $q$ depends (not explicitly) on the $k_{on}$ rates of both receptors, and their relative levels of expression. They take $k_{off,\ wt} = 3.5\exp\left(\frac{\sigma F_b}{kT}\right)$ from Doggett et al. (2002). Then to estimate $k_{off,\ mut}$, they solved

$$\sum i = 1^N \frac{(1-q)\exp(-k_{off,\ mut}t_i)(1-k_{off,\ mut}t_i)}{qk_{off,\ wt}\exp(-k_{off,\ wt}t_i) + (1-q)k_{off,\ mut}\exp(-k_{off,\ mut}t_i)} = 0.$$

Values of $q$ were sampled over the range of possible values ($0 \le q \le 1$) and a value of $k_{off,\ mut}$ was calculated for each value of $q$. Then they selected the $(q, k_{off,\ mut})$ pair that gave the best fit to the data.

For Model 3, multiple bonds of either type can form. In this case, the distribution of pause times doesn't have a simple expression, so they used MC simulations for many different $(q, k_{off,\ mut})$ pairs and selected the one with the best fit.

As in Doggett et al. (2002), the simulation starts with a single GP1b-vWF bond. The GP1b in this bond is wild-type with probability $q$ and mutant with probability $1-q$. Then 4 (or 5) things can happen in a time interval $dt$:

1. A WT GP1b-vWF bond can break ($P_1dt = k_{off,\ wt}n_{wt}dt$),

2. A mutant GP1b-vWF bond can break ($P_2dt = k_{off,\ mut}n_{mut}dt$),

3. A WT GP1b-vWF bond can form ($P_3dt = k_{on,\ wt}X_{A1}X_{wt}dt$),

4. A mutant GP1b-vWF bond can form ($P_4dt = k_{on,\ mut}X_{A1}X_{mut}dt$),

5. if there are no bonds, the bead can leave ($P_5dt = \gamma_w\delta_{n,0}dt$). It isn't clear if this is part of their simulation, but it is includeded in their previous paper.

## 3 Results Overview

Similar to their previous paper, they collected data on platelet accumulation, translocation velocity, frequency of bead thethering, and pause times at variable wall shear rates. They estimated $k_{off,\ mut}$ for each shear rate based on Model 1, and then estimated $k_{off}^0$ and $\sigma$, the parameters in the Bell model:

$$k_{off}(F) = k_{off}^0 \exp\left(\frac{\sigma F}{kT}\right).$$

In comparing their three hypothetical models, they found that Model 1 was most consistent with the experimental data. Finally they compared the kinetic parameters of the GP1b-vWF bond in 2B vWD with PT vWD and found no significant difference between these two bonds.

## Summary

This paper extends the analysis developed in Doggett et al. (2002) to the case where there are two different receptors in a platelet. While I'm not so interested in the biological conclusions of this paper, this framework may be useful in modeling platelet priming by agonists that act through multiple receptors.

## Reference

Doggett, T. A., Girdhar, G., Lawshé, A., Miller, J. L., Laurenzi, I. J., Diamond, S. L., and Diacovo, T. G. (2003). Alterations in the intrinsic properties of the gpib$\alpha$-vwf tether bond define the kinetics of the platelet-type von willebrand disease mutation, gly233val. *Blood*, pages 152–160.

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