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OneStep® Lead Characterization of High Affinity Biologic Interactions

Stuart Knowling, Sartorius, Fremont, CA

Correspondence
Email: octet@sartorius.com

Abstract

Biopharmaceutical drug discovery and development have celebrated the approval of breakthrough treatments in diseases of inflammation, cancer, and infectious disease in recent years. As the biopharma industry sees more therapeutic successes, the problems left to solve in medicine will prove increasingly more difficult. Protein therapeutics, or biologics, are known for having good specificity for their therapeutic targets and this often affords fewer side effects than small molecule drugs. Biologics are a viable route for targeting protein–protein interactions, cell surface receptors, and other difficult-to-drug therapeutic targets. The discovery process for biologics has been well established, especially for common molecular classes such as monoclonal antibodies, and newer classes of biologics are being sought for enhanced cell uptake, membrane permeability, and serum half-life. This application note demonstrates how the Octet® SF3 system with OneStep® Injections allows users to determine kinetics and affinity for high affinity biologics from a single analyte concentration. Analysis of high affinity biologics is important for lead selection and predicting the efficacy of protein therapeutics and therefore, with the ability to measure dissociation periods for up to 12 hours, the Octet® SF3 allows users to accurately assess high affinity protein therapeutics from the earliest lead selection stages onwards without the need for orthogonal assays.

Introduction

The process for biologics drug discovery from hit to lead involves screening (primary, secondary, and tertiary) to identify hits, followed by lead characterization including target binding characterization. Primary screening techniques for biologics normally focus on speed and throughput to identify hits from libraries containing 10^4–10^5 crude protein samples. Traditionally, primary screening has been performed with ELISA, biochemical assays, and/or label-free techniques such as the BLI-based Octet® systems. Secondary and tertiary screens can be used to further test the hits for functional binding effects or cross-reactivity. Once a panel of advanced hits has been compiled, they can be expressed and purified in small scale for in depth characterization before *in vivo* testing.

Target binding characterization is an important analytical step for the selection of high affinity (K_D <1 nM) and highly specific biologics regardless of the types of molecules. Kinetic analysis further describes the components of association and dissociation that comprise the overall affinity interaction. A biologics discovery lab may have two lead candidates with similar affinity (K_D) but their differences in kinetic rate constants of association and dissociation can be used to estimate which will be more useful *in vivo*. Accurate analysis of these kinetic rate constants is therefore important information for lead selection and predicting the efficacy of protein therapeutics.

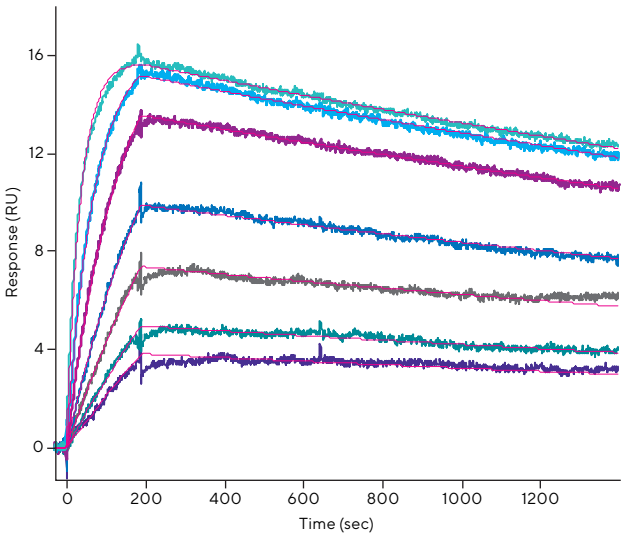
The Octet® SF3 system from Sartorius improves the efficiency of the characterization process over traditional SPR by determining the kinetics and affinity in a single step. OneStep® gradient injection are a unique feature on the Octet® SF3 system and dramatically increases the speed of affinity characterization while maintaining accuracy and high confidence in results. In this application note, we explore the utility of OneStep® Injections in kinetic characterization of biologics in both research and drug discovery.

OneStep® Determines Accurate Kinetics and Affinity from a Single Analyte Concentration

Traditional multi-cycle kinetic (MCK) analysis of biomolecular interactions with SPR techniques involves the testing of different concentrations of analyte in solution binding to the immobilized ligand. Each analyte concentration must be injected over the immobilized molecule briefly (1–10 min each) and then dissociation of bound analyte must be monitored under running buffer flow. Complex formation is observed as a function of time and at known analyte concentrations to determine the rate constants of association (k_a) and dissociation (k_d) and the equilibrium dissociation constant (K_D). An example of this analysis is shown in Figure 1 where seven concentrations of analyte are injected over an immobilized ligand to observe the time-resolved and concentration-dependent interaction parameters. Global kinetic analysis is performed by least-squares fitting a kinetic model to the binding data to find the best-fit values for k_a, k_d, and R_{max}.

The data in Figure 1 show that seven concentrations spaced two-fold apart are required to effectively test the 'kinetic space' of this interaction and determine the association and dissociation rate constants. Traditional SPR requires researchers to prepare a dilution series of analyte that is subsequently injected one after the other — adding preparation and analysis time to the workflow and increasing the potential for pipetting errors and evaporation. This can lead to erroneous estimates of the concentration of the binding partner in solution, which affects the accuracy of k_a, and subsequently the accuracy of K_D.

Figure 1
Traditional Multi-cycle Kinetic (MCK) Analysis of Analyte Binding to an Immobilized Ligand with Seven Concentrations of Analyte.



In contrast, OneStep® Injections are a powerful method to determine the kinetic and affinity parameters of a binding interaction using only a single sample of analyte and one injection. OneStep® Injections take a sample of known concentration and disperse it through a volume of running buffer (held within the OneStep® capillary line) as it is flowed to the sensor chip surface. This method, based on Taylor dispersion[1], produces a sigmoidal concentration gradient of analyte in the capillary fluidic line (Figure 2). As the sample gradient flows from the capillary to the sensor chip, binding data are collected in real time incorporating the full range of analyte concentrations presented to the surface from low to high.

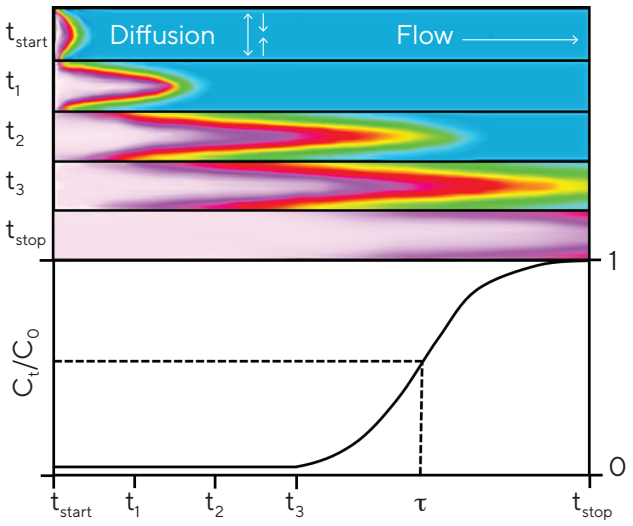
For OneStep® Injections, the analyte concentration at the flow cell over time is described by the Taylor dispersion theory as a function of the analyte diffusion coefficient, flow rate, and dispersion line geometry. The Octet® SF3 Octet® SPR Discovery Analysis Software automatically recognizes OneStep® Injections and calculates the analyte concentration over time using the system-given constants (flow rate, geometry data, and analyte diffusion coefficient). As an internal control for the gradient dispersion process, an injection of a bulk standard, typically 3% sucrose, dissolved in the assay buffer is performed in each OneStep® assay to ensure proper gradient formation is occurring and to calibrate for buffer viscosity. The result is a binding response with kinetic curvature which defines the association (k_a) and dissociation (k_d) rate constants when analyzed as a function of time and concentrations, as shown in Figure 3.

A basic requirement for conventional kinetic characterization is the observation of time-dependent binding of multiple, constant analyte concentrations to accurately determine k_a and k_d. OneStep® Injections accomplish this requirement in a single injection by measuring the time-dependent binding of analyte where concentration is also time-dependent. OneStep® binding data therefore gives the time- and concentration-dependent information required to determine k_a and k_d for a binding interaction in a single injection. Table 1 shows the kinetic rate constants and equilibrium dissociation constants calculated from the data in Figure 3 (OneStep® Injections) and Figure 1 (dose response) using the 1:1 kinetic model.

The comparison between the traditional injection method and the OneStep® method show good agreement in the kinetic rate constants (<20% difference) and the equilibrium dissociation constants (<1% difference)[2] determined for a nanomolar affinity interaction. Other comparisons of OneStep® Injections with traditional multi-cycle kinetics have shown good agreement for interactions up to high

Figure 2

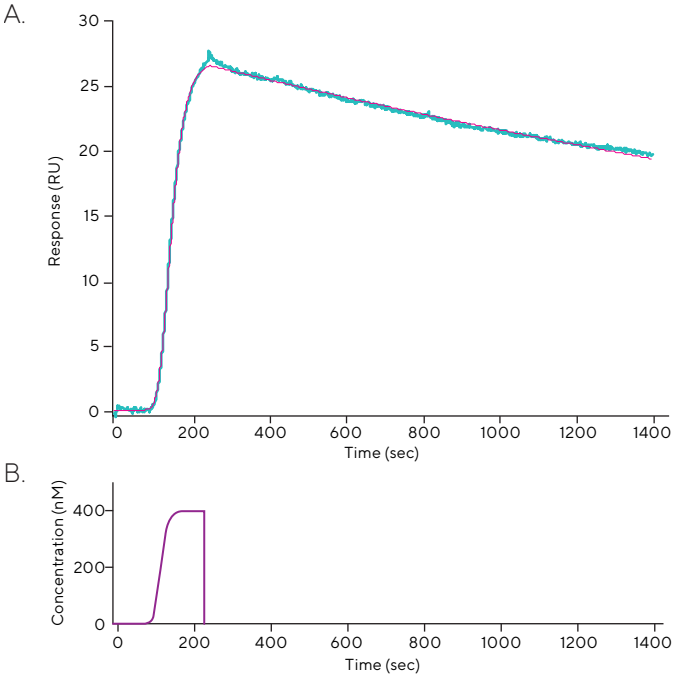
OneStep® Gradient Injections Create an Analyte Concentration Gradient of at Least 3 Orders of Magnitude from a Single Analyte Concentration.



Note. OneStep® gradient formation in the injection line (top panel), with the corresponding analyte concentration measured within the flow cell (bottom panel). Blue color indicates the running buffer and pink color indicates the analyte. The gradient formation and its relationship to analyte concentration at the flow cell is illustrated using five simulated snapshots (t_{start} – t_{stop}) of the injection line at different times, and shows that a single injection can be used to assess a full analyte concentration series.

Figure 3

OneStep® Binding Curve of Analyte Binding Immobilized Ligand.



Note. (A) OneStep® Binding data is shown in teal and the 1:1 kinetic model curve is shown in red. (B) The analyte concentration gradient of 0–400 nM is created from a single analyte concentration during a OneStep® Injection.

micromolar[3,4] affinity. Characterization with the OneStep® method required one sample versus seven samples with the traditional method. In addition, the OneStep® injection completed in roughly one-seventh the time required for the traditional method (Table 1).

Octet® SF3 systems can perform either traditional multi-cycle kinetics or OneStep® Injections to characterize kinetics and affinity. However the OneStep® method offers distinct advantages, saving time, reagent, and labor, without compromising data accuracy or reproducibility.

Octet® SF3 and OneStep® Basics

The Octet® SF3 system is a fully automated SPR system in which flow cells can be addressed individually or collectively for immobilization or in series for analyte characterization, enabling in-line reference subtraction. Samples are stored in temperature-controlled sample racks (4–40 °C) using either borosilicate glass vials or standard 96- or 384-well microplates, and up to 768 samples can be assessed in an unattended single run. Sample delivery to the sensor is achieved using an XYZ autosampler and the buffer tray can hold up to three one-liter bottles, comprised of one water and two buffer lines. Both buffer lines function independently and are degassed in-line, allowing two running buffers to be used during an assay. The fluidic system is comprised of tubing optimized for durability and chemical resistance. Tubing is connected to switching router valves that have excellent lifetimes, offering years of usage without required parts replacement. Simple method design enables setup for standard inject types or Octet® SF3-unique injections (*i.e.,* OneStep®, NeXtStep™, etc.) in a common workflow with the Octet® SPR Discovery Software.

OneStep® Assay Design to Characterize Advanced Hits for Lead Selection

Kinetic characterization of biologic advanced hits can be performed in several assay formats depending on the valency of the molecules and their ability to be specifically captured on a sensor chip surface. The following examples provide assay design guidelines and tips to make optimal use of OneStep® Injections for kinetic analysis on the Octet® SF3 system.

Figure 4
The Octet® SF3 Platform Allows Streamlined Analysis Through a Combination of Several Key Hardware and Assay Attributes.

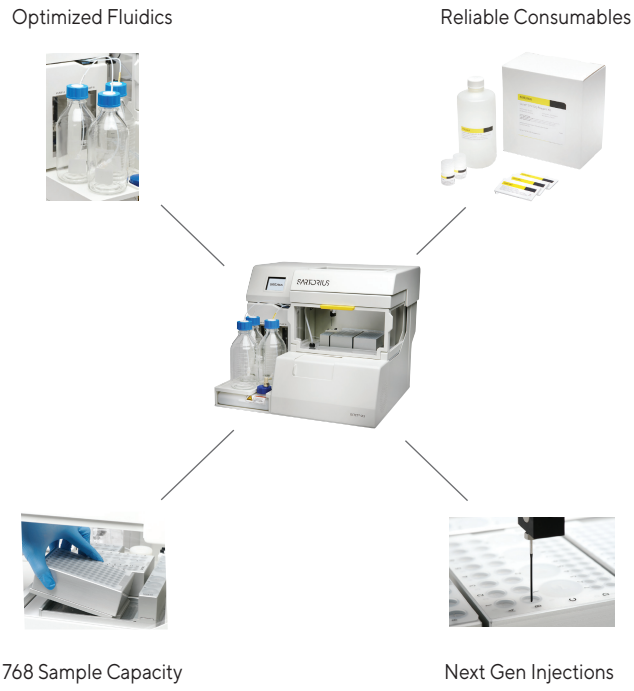


Table 1
Comparison of Kinetics and Affinity Characterization Results with OneStep® and Multi-cycle Kinetics Methods.

Method	k_a (x10^4 $M^{-1}s^{-1}$)	k_d (x10^{-4} s^{-1})	K_D (nM)	Sample Required (µl)	Characterization Time Per Analyte (hrs)
OneStep® Injections	9.46±0.01	2.717±0.002	2.874±0.004	150	0.68
Multi-cycle kinetics	7.14±0.01	2.054±0.002	2.878±0.006	400	4.73

Kinetic Characterization with Biologic as Analyte

One standard assay format is to immobilize the target and test the biologic (IgG, Fab, Fv, etc.) binding as the analyte as illustrated in Figure 5. The method of target immobilization can be either irreversible (amine, biotin, or thiol coupling) or reversible using an affinity tag (His-tag, Fc-tag, or other anti-tag capture). Flexibility in immobilization method is helpful as some targets may require specific conditions to maintain activity during and after the immobilization process. In the example shown in Figure 7, the target was immobilized via amine coupling and a simple regeneration of the surface with 10 mM HCl was used after each binding cycle.

Table 2 gives general method design guidelines for OneStep® assay protocol steps. If the ligand is captured using a reversible method, such as with an affinity tag or capture ligand, then an optional capture injection assay step can be used to capture fresh ligand (Experiment Step #3 in Table 2). Following OneStep® Injection of analyte the captured ligand is removed at the end of each cycle using a regeneration step, allowing subsequent ligands to be captured for analysis.

Figure 5

Illustration of Immobilized Antigen Binding Biologic (IgG) as Analyte.

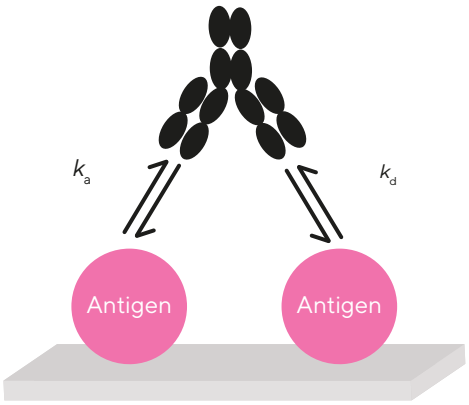
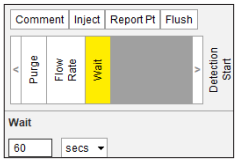


Table 2

Assay Design Guidelines for Kinetic Characterization with OneStep® Injections.

Assay Step	Protocol Method Settings	Notes
General and Periodic Assay Settings	▪ Replicates: 2–3 ▪ Sample rate: 5 Hz ▪ Periodic cycles: ▪ Blank cycles: periodic, every 3 cycles ▪ Startup blanks: 5–10 ▪ Bulk std. cycles: 1 	Duplicate injections are recommended for most characterizations. 5 Hz data sampling provides good resolution for the association phase while maintaining minimal file size for long assays.
Assay Pre-cycle	▪ Purge ▪ Flow rate ▪ Wait: 60 sec 	Pre-cycle features that are placed in the cycle editor are automatically performed before each analyte injection (Detection Start). Purging of the fluidics washes out any remaining sample from the previous cycle. Setting the flow rate ensures the analyte inject flow rate is configured and the wait allows a 1 min period for baseline stability prior to starting the cycle.
Capture Injection (optional)	▪ Inject: ▪ Inject volume/flow rate (per assay development) ▪ Flow path: typically FC 1 or FC 3	Optional ligand capture injection for fresh immobilization of ligand in each cycle. Ligand solution must be stable for the duration of the assay. Concentration, inject volume, and flow rate are determined during assay development and optimization. Use a dummy or buffer inject for the sucrose cycle (S1).
Analyte Injection	▪ OneStep®: ▪ Flow rate: 50 µL/min ▪ Flow path: FC 1-2-3 ▪ Sample volume: 75% of loop for moderate affinity and 100% of loop for high affinity ▪ Dissociation: 300 sec minimum, (30 sec for Sucrose Cycle)	Requires at least 250 µL of analyte solution for 2 replicates. Sucrose Cycles (S1) need minimal dissociation as only data from the association phase are used.
Regeneration Injection	▪ Inject: ▪ Inject volume/Flow rate: typically 25 µL at 50 µL/min ▪ Flow path: typically FC 1-2-3 ▪ Dissociation: 60 sec	Regeneration scouting and validation is a common part of assay development and optimization. The general regeneration suggestion is to use the shortest injection times that efficiently regenerate the surface to retain ligand/surface activity.

The assay design guidelines can be modified to suit the nature of different samples, target molecules, ligand capture method, or other experimental variables.

The assay method designed in Figure 6 was performed with 10 Fab hits injected using the OneStep® method and a simple 1:1 kinetic model was fit to the data via non-linear least squares fitting.

Ten Fabs (of advanced hits) binding to the immobilized target were characterized using OneStep® Injections with binding traces are shown in in Figure 7, with the goal of selecting the best candidates for lead optimization. The best-fit values for association and dissociation rate constants from the results in Figure 7 were presented in an affinity plot (k_d vs k_a) to visualize the kinetic differences of each Fab binding target (Figure 8).

The affinity plot (Figure 8) helps visualize how kinetics comprise affinity and to compare both kinetics and affinity of hits. OneStep® Injections capture this level of information from a single injection per analyte. The OneStep®-derived kinetics of biologics can be reviewed with other important biophysical and functional properties to select a lead or leads to optimize.

Figure 6

Octet® SPR Discovery Software Showing the OneStep® Injection of Biologic Hits in OneStep® Kinetics Protocol.

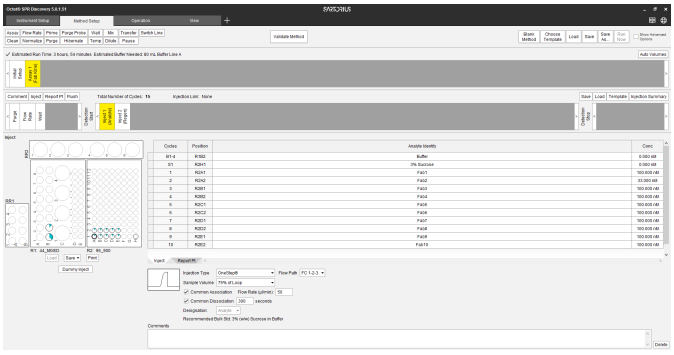
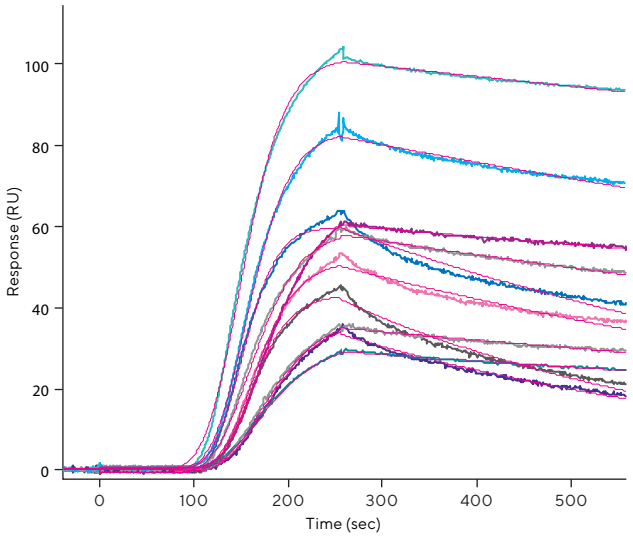


Figure 7

OneStep® Kinetic Characterization of Biologic Advanced Hits for Lead Selection.

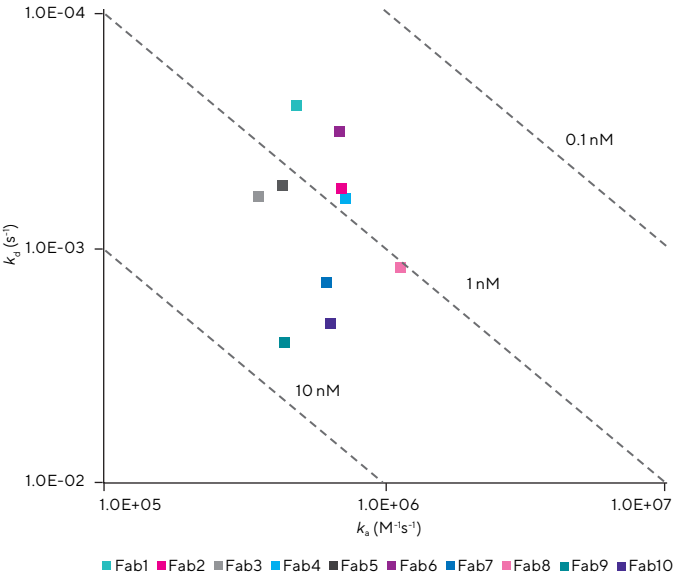


4 hrs	Time required for the OneStep® protocol including buffer blank and a sucrose cycle
25 hrs	Time required for the traditional dose response protocol including 7 analyte concentrations and buffer blank cycles

Note. Assay format is biologic (Fab) as analyte. Binding data are least-squares fit with the simple 1:1 kinetic model (fitted curves shown in pink).

Figure 8

Affinity Plot (k_d vs k_a) for Biologics Binding to Immobilized a Target Characterized by a OneStep® Assay.



Note. Dashed lines indicate common affinity relationships with different kinetic rate constants.

Kinetic Characterization with Target as Analyte

A second characterization assay format is to immobilize the biologic(s) to the sensor surface and bind the target in solution (Figure 9). This approach can be easily applied to biologics which have common domains that serve as a capture epitope, such as the Fc domain on IgG. Immobilizing the biologic is also beneficial if the molecule is multivalent or if the target is unstable when immobilized. Capture of IgG can be accomplished by pre-immobilizing an anti-Fc antibody or a recombinant Protein A or G on the sensor surface via amine coupling. These capture molecules can be used to capture IgG and orient the captured IgG to bind target in solution. Other specific capture antibodies can be used when biologics are not immunoglobulins. Regeneration of the biologic from capture antibody or Protein A may require injection of 10 mM glycine HCl pH 1.5 or 3 M $MgCl_2$, while regeneration of IgG from Protein G may require injection of 10 mM NaOH, with appropriate assay development and optimization as needed.

The example for target as analyte kinetic characterization in Figure 10 uses an anti-Fc antibody to capture IgG biologics (not shown) followed by a OneStep® Injection of target over each captured biologic.

The best-fit kinetic rate constants from the characterization example in Figure 10 were plotted in the affinity plot, Figure 11. Kinetic rate constants derived from this OneStep® characterization can be combined with other biophysical and functional data to select the best biologic hits to progress.

Figure 9
Illustration of Immobilized Biologic (IgG) Binding Antigen as Analyte.

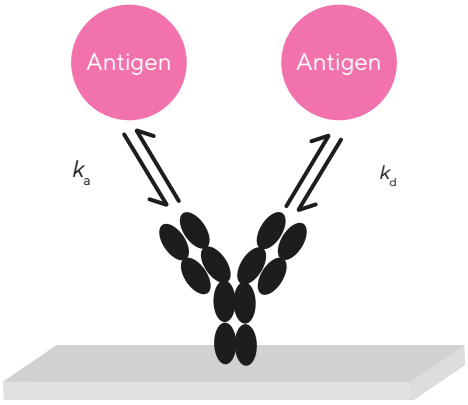
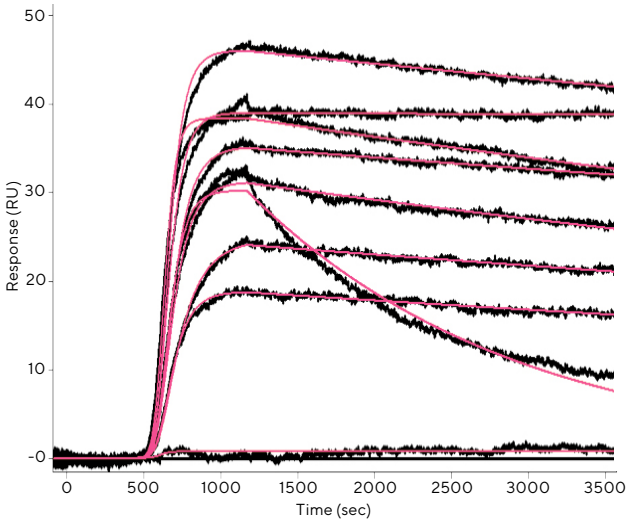


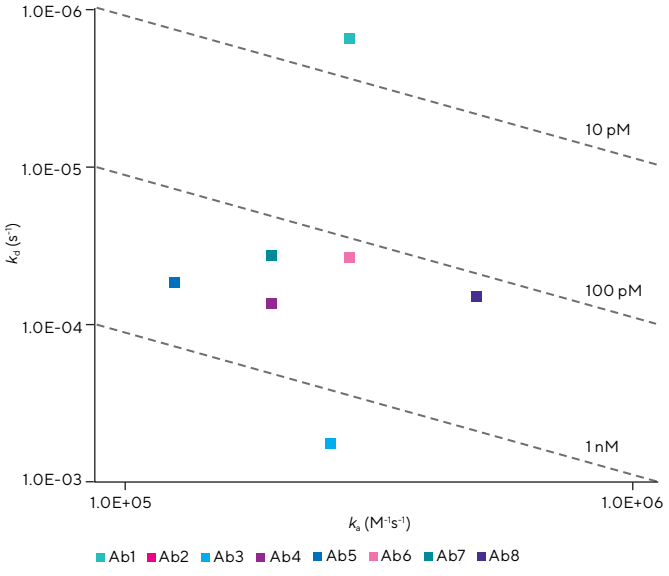
Figure 10
OneStep® Kinetic Characterization of Biologic Advanced Hits for Lead Selection.



20 hrs	Time required for the OneStep® protocol including buffer blank and a sucrose cycle
63 hrs	Time required for the traditional dose response protocol including 7 analyte concentrations and buffer blank cycles

Note. Binding data (black curves) are least-squares fit with the simple 1:1 kinetic model (fitted curves shown in pink).

Figure 11
Biologic-Immobilized Affinity Plot.



Note. Affinity plot (k_d vs k_a) for target binding immobilized biologics characterized by OneStep® assay. Dashed lines indicate common affinity relationships with different kinetic rate constants.

OneStep® Injections can characterize binding interactions to determine the important kinetic and affinity constants for making informed lead selections using either the biologic or target as analyte assay formats. Once a lead is selected, the next phase of drug discovery includes lead optimization and in-depth characterization. The target as analyte assay format is often chosen where humanization (if required) and affinity maturations are performed to optimize the target binding properties of a lead.

Determining Accurate Dissociation Rate Constants

As biologic hits are progressed to leads the potencies and especially the binding residence time increases, requiring long dissociation times for typical SPR analysis. Interaction residence time, defined as the inverse of the dissociation rate constant ($1/k_d$), may be reported in seconds, minutes, or hours for very potent molecules. When residence time is measured in hours, it is important for the analytical technique to provide stable measurements for these lengths of time. It has been previously shown that a dissociation event of 5% or more of bound complex is key to accurate measurement of dissociation rates for label-free assays.[5] The assay must therefore be stable and sensitive to changes in response equal to 5% of equilibrium response (R_{EQ}) over the course of 5+ hours in certain cases (it is preferable that a visual drop in the response is also observed in addition to a mathematical decrease of 5% prior to performing regeneration). As shown in Table 3, the minimum time to measure dissociation increases dramatically between 10^{-5} and 10^{-6} s^{-1}.

Table 3
Minimum Required Dissociation Times by Dissociation Rate Constant.

k_d (s^{-1})	Time to 5% Dissociation
10^{-3}	51.3 s
10^{-4}	8 m 33 s
10^{-5}	1 h 25 m
10^{-6}	14 h 15 m

In characterizations of interactions with slow dissociation rate constants the assay design must be adjusted to collect accurate data while maintaining practical run times. Buffer blank injections must be performed to reference any drift of the immobilized molecule for the same cycle length as the analyte injection. Instrument baseline stability must also be consistent and reproducible for multi-hour recordings stressing the stability of temperature and buffer flow control of the SPR system. In the next section we will address these aspects of high affinity measurements using examples of OneStep® analysis of slow dissociation interactions.

Simplifying High Affinity Lead Characterization with OneStep®

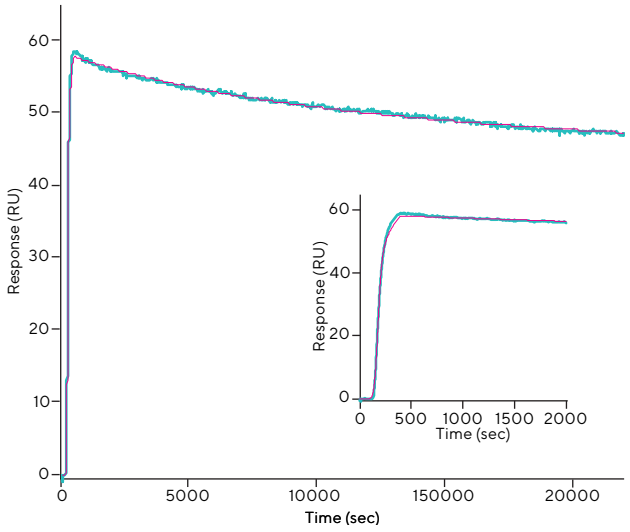
High affinity characterization with OneStep® Injections requires system and sensor stabilization time, appropriate gradient design, and sufficient dissociation time (see Table 3). For best results, the Octet® SF3 should be cleaned using the Desorb and Decontaminate program in the Octet® SPR Discovery Software using the Octet® SPR Maintenance Kit (19-0137), and a new sensor chip should be installed after cleaning. The method of immobilization chosen should be irreversible or very high affinity, such as biotin-streptavidin, to avoid long-term dissociation of the immobilized molecule. The analyte solution for OneStep® Injections should be ~100X the expected K_D and the dissociation time should be long enough for at least 5% dissociation of the bound analyte.

The first high affinity example (Figure 12) is a complex kinetic case where both the biologic and target are bivalent. The biologic lead with biotin tag was immobilized via biotin capture to a low surface density (50 RU), and the sensor allowed to stabilize for 1 hour. The assay protocol design for this characterization was constructed so that the lead was immobilized prior to the kinetic assay and without regeneration.

Startup Cycles injections are common in SPR-based kinetic assays to obtain the best injection reproducibility and referencing, however in high-affinity assays with multiple-hour dissociations they must be truncated for practicality. In this example, the first two blanks are dissociated for 6000 sec to stabilize the sensor and the third blank and analyte injection have the full dissociation time of 21,600 sec (6 hours). This design allows the injection system and sensor chip to give the most reproducible and stable signal for referencing the 6 hour dissociation event. Therefore, the third blank is used as the reference for the full binding and dissociation curve recorded during the analyte inject.

Figure 12

OneStep® Kinetic Characterization of a High Affinity Bivalent Biologic-target Interaction.

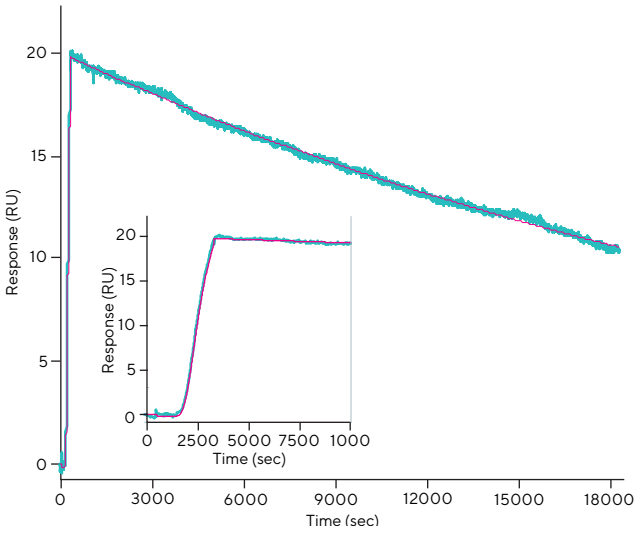


17 hrs	Time required for the OneStep® protocol including buffer blank and a sucrose cycle
63 hrs	Time required for the traditional dose response protocol including 7 analyte concentrations and buffer blank cycles

Note. Figure inset shows the first 2000 sec of data including the full OneStep® association (0–400 sec) and the first 1600 sec of dissociation. Binding data are shown in teal and the fitted model curve in pink.

Figure 13

OneStep® Kinetic Characterization of a Simple High Affinity Biologic-target Interaction.



15 hrs	Time required for the OneStep® protocol including buffer blank and a sucrose cycle
54 hrs	Time required for the traditional dose response protocol including 7 analyte concentrations and buffer blank cycles

Note. Assay format is target as analyte and dissociation time is 5 hours. Figure inset shows the first 1000 sec of data including the full OneStep® association.

The assay was performed in this first example in which 100 nM target solution was injected with the OneStep® method using 100% sample loop volume, a flow rate of 30 µL/min, and dissociation was monitored for 6 hours. Data was double reference subtracted and analyzed with the bivalent analyte kinetic model as the target and biologic were both bivalent. The data and best-fit model curve are shown in Figure 12.

The first high-affinity characterization example of target binding immobilized biologic shown in Figure 12 gave best-fit values of 4.552 (±0.007) x10^{5} $M^{-1}s^{-1}$ for k_a and 5.75 (±0.02) x10^{-5} s^{-1} for k_d for the primary (1:1) interaction. The observed affinity (K_D) for the 1:1 interaction (the initial binding event) was 126.4±0.5 pM. Approximately 19% of the bound target was observed to dissociate during the 6 hour measurement which exceeds the minimum analysis requirement of 5%. Complex kinetic cases such as this bivalent example normally pose a challenge for standard SPR analyses but with the high-concentration resolution of OneStep® assays, the bivalent analyte model is fit to the data to easily determine the kinetics of the interaction. The concentration resolution of the OneStep® method refers to the continuous concentration gradient wherein every time point during the injection tests a different concentration within a range of 3–4 orders of magnitude. The enhanced kinetic resolution of OneStep® assays will be useful as more complex therapeutic mechanisms are explored in the future.

The second high-affinity example (Figure 13) is a simple 1:1 interaction using the target as analyte assay format, where 120 RU of biotin-tagged biologic was captured. 100 nM of target analyte was injected using a OneStep® injection with 100% of sample loop volume at 40 µL/min with a 5-hour dissociation.

The high-affinity characterization example shown in Figure 13 gave best-fit values of 9.21 (±0.09) x10^{4} $M^{-1}s^{-1}$ for k_a and 3.500 (±0.001) x10^{-5} s^{-1} for k_d. The observed affinity (K_D) for the interaction was 380±4 pM. Nearly 50% of bound target was observed to dissociate in the 5 hour dissociation period.

Conclusion

Scientists in the biologic drug discovery space are constantly identifying new therapeutic targets and seeking new molecules to combat disease. As new hits are generated and optimized into lead candidates, the Octet® SF3 with OneStep® gradient injections can accurately characterize target binding for panels of advanced hits all the way to high affinity leads.

- OneStep® characterization is 3- to 6-fold faster than traditional characterization on a 4-channel SPR system.
- OneStep® Injections use less sample (50% less analyte).
- No analyte dilutions required.
- No major adjustments to workflow — current affinity characterization workflows easily migrate to OneStep® assays from traditional methods.

New classes of biologics with complex binding mechanisms are also more easily analyzed with the higher analytical resolution of OneStep®. The OneStep® method relies on the robust principles of Taylor dispersion and can be used to confidently determine kinetics and affinity from a single gradient injection. The Octet® SF3 platform provides excellent baseline stability for accurate kinetics characterization of high affinity binding interactions. Baseline stability coupled with the time and injection reducing advantages of OneStep® make the Octet® SF3 an optimal system for high affinity biologic characterization.

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Germany
Sartorius Lab Instruments GmbH & Co. KG
Otto-Brenner-Strasse 20
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Corporation
565 Johnson Avenue
Bohemia, NY 11716
Phone +1 888 OCTET 75
Or +1 650 322 1360

For further contacts, visit
www.sartorius.com/octet-support

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