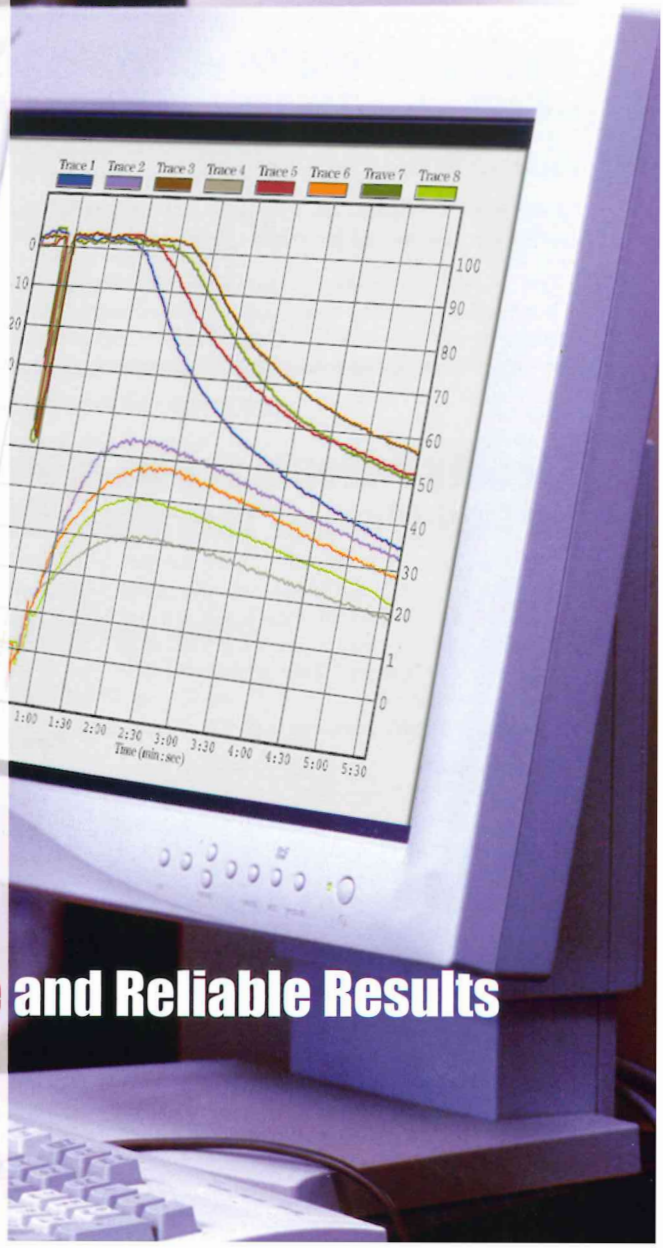
CHRONO-LOG
CORPORATION

Advancing the Clinical Detection of Hemostatic Abnormalities



CHRONO-LOG Model 700

Whole Blood/Optical Lumi Aggregometer

- Easy to Use with Rapid Results
- Whole Blood and Optical Aggregation Modes
- Disposable and Reusable Impedance Electrodes
- Simultaneous ATP Secretion Studies
- Dual and Four Channel Systems

A Proven Track Record of Accurate and Reliable Results

CHRONO-LOG
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The Answer to Your Platelet Function Testing Needs

Rapid and Simple Screening

Chrono-log Whole Blood/Optical Lumi-Aggregation Systems improve detection of abnormal platelet function by simultaneously measuring platelet aggregation and dense granule secretion in a physiologic whole blood environment or traditional plasma sample. In addition to optical aggregation, the turbidometric feature permits platelet function testing for the Ristocetin Cofactor Assay and Sticky Platelet Syndrome tests.

Efficient and economic, the simplicity and heightened sensitivity of whole blood testing in the Clinical Laboratory permits the establishment of a therapeutic monitoring program:

- Monitor aspirin therapy to determine response or non-response with Collagen-induced aggregation in whole blood.[38-41]
- Monitor Plavix therapy with ADP-induced aggregation in whole blood.[42,43]
- Monitor administration of DDAVP by Ristocetin-induced aggregation in whole blood.[2-4,8]
- Measure effect of GPIIb/IIIa receptor blockage and other anti-platelet drugs.[31]

Identify Patients at Risk of Thrombosis or Bleeding... Select Patients for Anti-Platelet Therapy... Monitor Dosage and Response

Patients with a previous history of thrombosis show a high prevalence of platelet hyperactivity. Where the goal of therapy is inhibiting platelet aggregation, Chrono-log Whole Blood Aggregometers can routinely identify patients at risk for thrombosis or bleeding and can verify effective treatment.[37] For example:

Aspirin (ASA) is used therapeutically to inhibit thromboxane production of circulating platelets. Measuring platelet aggregation in whole blood with low and high Collagen concentrations (1 and 5 ug/mL) is a cost-effective, quick screen for monitoring effective dosage levels of ASA. While low Collagen concentration at 1ug/mL can best detect the aggregation defect caused by ASA,[36] the high Collagen concentration of 5ug/mL bypasses the ASA effect, serving as an auto-control and allowing the level of response to be determined. Poor aspirin response is defined as >50% of platelets aggregating when the 1ug/mL is compared to the 5ug/mL test.[38-41-45] Using this criteria with whole blood aggregation, in a study of 122 patients being treated with ASA for secondary stroke prophylaxis, 77% of those defined as ASA resistant experienced a new stroke or TIA.[45] In a separate study, thromboxane-dependent ATP release measured with Luminescence, volunteers who ingested ASA within the previous 48 hours, exhibited reduced ATP release with both low and high Collagen concentrations.[18]

Plavix (Clopidogrel) inhibits the binding of ADP to its receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, inhibiting platelet aggregation. When testing in whole blood with 20 uM ADP, a 57-60% mean dose dependent inhibition of platelet aggregation was seen one day after a loading dose of 600 mg Clopidogrel was administered.[43] Following ten days of treatment with 75 mg Clopidogrel, whole blood aggregation with 2.5 and 5 uM ADP was absent while tests with ADP at 10 and 20 uM showed "markedly impaired aggregation." Optical aggregometry with PRP and ATP secretion remained normal.[42] Published in 2006, 5 uM ADP is used to test for Clopidogrel response in Whole Blood... ≤5 Ohms of aggregation is a responder, whereas, >5 Ohms reflects a nonresponse. MeSAMP, a $P2Y_{12}$ receptor blocker, is used to maximize inhibition in determining pharmacokinetic or pharmacodynamic resistance.[46] Thus, Whole Blood Aggregometry with ADP is an effective and useful test to screen for Clopidogrel response.[42, 46]

The GPIIb/IIIa receptor antagonist abciximab (ReoPro™) inhibits platelet function by preventing the binding of fibrinogen and von Willebrand factor to activated platelets. Whole Blood Impedance aggregation with 5ug/mL Collagen more closely parallels receptor blockage than turbidimetric aggregation with 5 or 20 uM ADP and is a rapid, simple and accurate method for measuring the effects of abiciximab.[32]

Dipyridamole (Persantin), a coronary vasodilator, antithrombotic drug, significantly inhibits aggregation in whole blood when testing with 3.5 uM ADP or 5 ug/mL Collagen; this inhibition is not seen in platelet-rich plasma. Interaction between platelets and red blood cells plays an important role in the anti-platelet activity of Dipyridamole.[19]

In a study noted above, it was concluded that: "The WB impedance assay should be widely used in the clinical practice to identify subjects who are resistant to aspirin and clopidogrel." [42]

CHRONO-LOG Model 700

Whole Blood/Optical Lumi Aggregometer

Measures platelet function on patient samples using electrical impedance in whole blood or optical density in plasma while simultaneously measuring ATP release by the luminescence method.

Comprehensive Diagnostic Capability

Platelet disorders shown below can be detected using Whole Blood/Optical Aggregometry and/or Luminescence:

von Willebrand Disease	Extracorporeal circulation	Deficiency of the enzyme cyclo-oxygenase
Glanzmann's Thrombasthenia	Heparin-Induced Thrombocytopenia	Deficiency of the enzyme thromboxane synthetase
Storage Pool Deficiency (SPD)	Sticky Platelet Syndrome	Thrombocytopenia with absent radii (TAR syndrome)
Thrombopathia or Thrombocytopathy	Bernard-Soulier Syndrome (BSS)	Risk of thrombosis
May-Heggelin Anomaly	Gray Platelet Syndrome	Membrane receptor site defects
Defective early responses (primary defects)	Secretion defects	
Non-steroidal, Anti-inflammatory drugs	Hyperaggregability	

Patients with histories suggesting hemorrhagic disorders are often investigated for coagulation defects rather than platelet dysfunction,[5] because optical aggregation studies are time-consuming and ambiguous. NOW, with less than 5mL of blood and in less time than it takes to prepare plasma for tests of coagulation,[5,6] you can detect a wide variety of platelet disorders.

For detection of vW disease, Ristocetin-induced platelet aggregation (R.I.P.A.) by the impedance method in whole blood, is a highly sensitive and time efficient method of screening persons at risk. While patients with von Willebrand disease exhibit the same abnormalities in whole blood as in platelet rich plasma, an extended lag phase of >70 seconds in whole blood allows for a clearer separation of vW patients from normals.[7,8] In addition, screening for Type 2B and Platelet-Type von Willebrand is quickly performed with low concentration Ristocetin.[44]

As impedance aggregometry in whole blood is a more adequate tool for the detection of platelet hyperaggregability than the optical method in PRP,[12] more patients can be identified as at risk for thromboembolic complications. This greater sensitivity results from performing tests in the presence of red cells and leukocytes.[13-15]

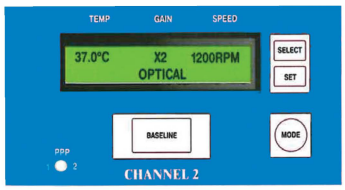
The electronic impedance technique can measure aggregation when optical methods cannot — in hemolysed, icteric or lipemic samples where the sample turbidity interferes with measurement, or in "giant" platelet syndromes where centrifugation results in the loss of the platelets to be studied.[28,29] Due to the small blood draw required for Whole Blood testing, [5 mL vs. 20 mL], pediatric patients can be tested for platelet disorders. Specific platelet defects have been diagnosed with platelet counts as low as 70,000/mm³ with pediatric patients.[3]

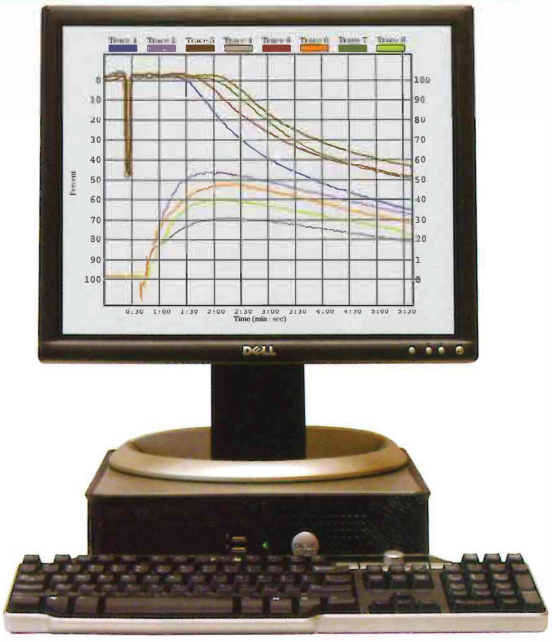
Direct measurement of ATP secretion via Luminescence in whole blood or PRP provides unequivocal evidence of normal dense granule release and is a quantitative measure of platelet activation.[9] In contrast, repetitive dose response optical aggregation tests in PRP failed to diagnose 67% of patients with Storage Pool Deficiency and a prolonged bleeding time.[10] Simultaneous measurements of the release reaction provides further insight into the mechanisms of platelet response.[11]

The CHRONO-LOG Model 700

Easy to Use... Rapid Results... Fast Turnaround Time

- Test Four Samples at One Time with Two Dual Channel Modules
- Two aggregation modes—Whole Blood (Impedance) and Optical (Turbidometric)
- Disposable and Reusable Impedance Electrodes
- ATP Secretion Studies (Luminescence)
- Push Button Controls
- LCD Display with System Error Monitoring for each Channel
- Built in Computer Interface
- AGGRO/LINK8 and vW Cofactor Software Packages Included





CHRONO-LOG Model 700

Whole Blood/Optical Lumi Aggregometer

Efficient and Economic

Chrono-log Whole Blood/Optical Lumi-Aggregation Systems allow the study of platelet function in whole blood in the presence of other cells, before the decay of labile modulators. A micro-sample of whole blood is all that is required for measurement of aggregation and secretion, making the Chrono-log System particularly suitable for research with smaller laboratory animals.[20-21]

The simultaneous measurement of aggregation with a secretion study simplifies, speeds and reduces the cost of your platelet function testing. In addition to saving time, less blood is needed, precious agonists are conserved and consumable costs reduced.

A Powerful and Flexible Research Tool (Three Systems in One)

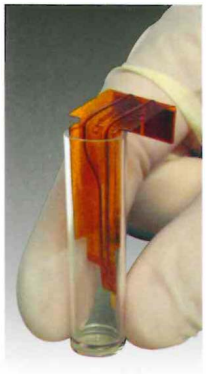
• Optical Aggregation

Optical (turbidometric technique)

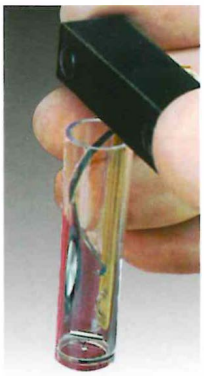
The Chrono-log Model 700 Aggregation Systems include automatic optical aggregation channels for measuring platelet or leukocyte aggregation in PRP or isolated samples, for measuring Ristocetin CoFactor Activity, and for measuring agglutination of latex particles or investigating shape change of suspended cells.

Dual-beam infrared light sources and photodiode detectors are used to determine the difference in light transmission between PRP and PPP, with the zero and full-scale baselines automatically set by a single pushbutton. A platelet count difference of only 50 x 10^9/L is needed for a full-scale deflection. Laboratory personnel can check the calibration of the optical circuitry and perform an auto-calibration, greatly reducing down time. This feature provides more reliable and accurate calculation, which is especially important in the calculation of Slope in the performance of the Ristocetin CoFactor Assay.

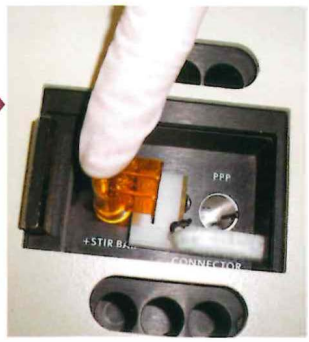
• Impedance Aggregation



Disposable Electrode



Reusable Electrode



• Luminescence

Sensitive Luminescence Technique

A sensitive photomultiplier tube in the Chrono-log Lumi-Aggregation Systems provides a voltage output proportional to the luminescence intensity. A wide variety of luminescent reactions (ATP release, total adenine nucleotides, superoxide generation and others) can be measured by a Chrono-log Lumi-Aggregation System.

Bio-Luminescence and Chemi-Luminesence Assays

• Adding CHRONO-LUME® Reagent to the sample provides the ability to measure platelet ATP Release. In addition to detecting Storage Pool and Secretion defects in the Clinical Laboratory, Luminescence is also a rapid and sensitive method for detecting Heparin-Induced Thrombocytopenia (HIT).[33]

• Addition of Luminol to a sample of Leukocytes provides the ability to measure Superoxides. Chemi-luminescence has been proven to be of value in the identification of neutrophil defects such as Chronic Granulomatous Disease and myeloperoxidase deficiency.[17]

White Blood Cells

[In the presence of leukocytes, platelet aggregation is amplified by the physiologic stimulus, platelet activating factor (PAF).]

• Chrono-log Whole Blood/Optical Lumi-Aggregometers can also be used for leukocyte function studies.[16,34,35] Leukocyte aggregation and superoxide generation can be measured simultaneously in a single sample of diluted blood or prepared leukocytes.

• Aggregation has also been demonstrated when leukocytes were activated by N-formyl-methionyl-leucylphenylalanine (fMLP) and leukotriene B_4 (LTB_4).[35] This data add to the possibility that the onset and propagation of inflammation, hemostasis, thrombosis and atherosclerosis might be influenced by platelet-leukocyte interactions.[24-26]

CHRONO-LOG Model 700

Whole Blood/Optical Lumi Aggregometer

Specifications

Chrono-Log Patented Electronic Impedance Technique

Chrono-log Whole Blood/Optical Lumi-Aggregation Systems detect platelet aggregation by passing a minute amount of electrical current between two electrodes immersed in whole blood, diluted blood, platelet rich plasma or washed platelets and by measuring the impedance between the electrodes. During initial contact with the sample, a monolayer of platelets forms on the electrodes. When an agonist is added there is gradual platelet aggregation at the electrodes, increasing the impedance.[21] The increase in impedance upon stimulation is directly proportional to the platelets aggregating onto the Electrode Probe Assembly.[22]

The Electrode Probe Assemblies have two carefully spaced rigid precious metal wires on which aggregation occurs. The Reusable probe (P/N 369) has a plug-in cable long enough to permit easy cleaning between samples by rinsing in water and saline. The Disposable probe is supplied in its own test cuvette and is disposed along with the sample, test cuvette and stir bar following completion of the test. P/N 315 Disposable Probes are for single use only and do not require cleaning.

The 700 Models include both the Reusable Probes (P/N 369) and Disposable Probes (P/N 315)

Test Channels:

(2) or (4) Channels (Two, 2-Channel Modules), with:
Impedance Aggregation - aggregation in a 1mL sample. Automatic baseline set at 0% and 20Ω gain fixed at 50%.
Optical Aggregation – aggregation in PRP, gel-filtered or washed platelet samples.
Luminescence - Photo-multiplier tube detects ATP Release. Nine gain settings - X 0.005 to X 2.

Front Panel Display and Controls:

LCD Display – 24-characters x 2-line Liquid Crystal Display, one per channel, displays:
- Heater Block - temperature in ^{O}C
- Luminescence gain
- Stirring speed in RPM
- Operating mode (Impedance or Optical)
- Warning messages

Power ON/OFF Switch
Set Baseline Pushbutton(s) - Sets the Aggregation and Luminescence baselines. For Impedance, adds 20 ohms (± 0.2 ohms) of resistance to set the impedance gain. For Light Transmission Aggregation, sets fu11 scale to 100%.
Select Switch – select Luminescence Gain, Temperature or Stirring Speed
Set Switch – Set Luminescence Gain, Temperature or Stirring Speed. *Mode Switch* – Set Impedance or Optical mode
PPP Selector Switch - Set to 1, tests referenced to Channel 1 PPP. Set to own channel (2,3,4), test referenced to PPP for that channel.
Calibration Switch – Key-activated calibration of optical circuits.
Heater Block - set between 35.0°C and 39.0°C in 0.1°C steps. Error detection prevents operation when outside ±0.2°C.
Stirrer - 400 to 1200 RPM in 100-RPM steps with "Stirrer Stopped" position. Error detection prevents operation if not within ± 10 RPM.

Sample Volumes

Whole Blood Lumi-Aggregation - typically 450µL whole blood plus 450µL of irrigation saline and 100µL CHRONO-LUME® Reagent.
Whole Blood Aggregation - typically 500µL whole blood plus 500µL irrigation saline
Optical Lumi-Aggregation - typically 450µL PRP plus 50µL CHRONO-LUME® Reagent; 225µL PRP plus 25µL CHRONO-LUME® with spacers
Optical Aggregation – typically 500µL PRP; 250µL with spacers

General Specifications *(each module)*

Power requirements - Switch selectable 115 or 230VAC (±10%), 50/60 Hz, 150 watts max.
Dimensions – 14" (36cm) wide, 8.5" (22 cm) high 18" (46cm) deep
Weight - 40 lbs. (18kg)
Incubation Wells – Six (6) wells each channel @ 36.5° ± 1.0°C when temperature set at 37°C.

Output Options:

Computer Interface - Digital Outputs - RS-232 and USB with AGGRO/LINK®8 software.
Data Reduction System – *(Included with Models 700-2DR and 700-4DR)* - State of the Art Computer and Color Printer.
Software packages, Installed:

WINDOWS 10 [subject to change]

AGGRO/LINK®8 - real time color display of 4 channels of aggregation and ATP release… *total of eight traces.* Computes amplitude, slope, lag time and area under the curve. Reagent data, test values, and demographics stored in computer for later recall. *[Requires Windows 7 or better operating system]*

vW Cofactor Software - on-screen instructions, best-fit standard curve and CD calculated for 2 to 6 points. Allows rerun or deletion of serial point. Stores curves with lot numbers. Four samples can be run simultaneously. Percent of vW activity calculated and reported.

Chart Recorder - Analog output. Chrono-log Model 708 Single or Model 709 Dual Pen recommended. Other recorders must have (1) megohm min. input impedance, 100 mV range and 1 cm/minute chart speed.

Accessories and Supplies - Impedance

Electrode Assembly [reusable] – P/N 369R (one for each channel)
Electrode Assembly [disposable] – P/N 315-25, P/N 315-50, P/N 315-100 (includes test cuvette)
Cuvettes – 1mL, P/N 367
Stir Bars – Disposable: siliconized, P/N 370; Reusable: Magnetic, Teflon-Coated, P/N 368

Accessories and Supplies – Optical

Insert Assembly – P/N 366 (one for each channel)
Cuvettes – 500µL, P/N 312
Stir Bars – Disposable: siliconized, P/N 311
Spacers, P/N 365, for testing microvolume samples as low as 250µL

U.S. Patent No 6,004,818; European Patent No. 1004020 protects these instruments; other Patents Pending

Windows is a trademark of Microsoft Corporation

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